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VIROLOGY

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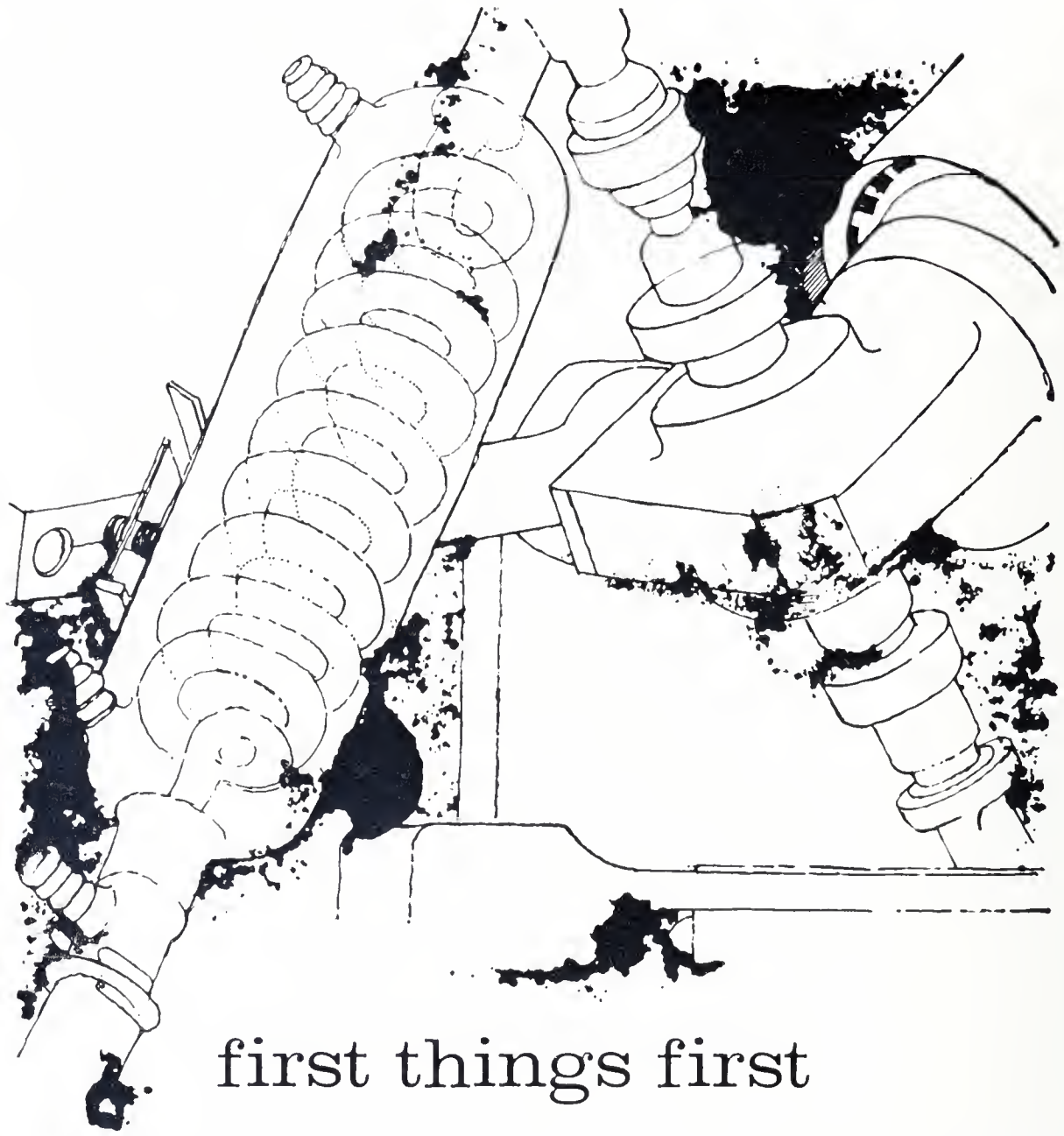

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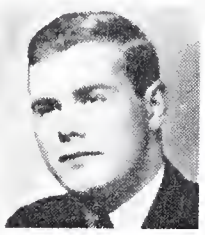

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Editorials

It is a common observation that medical science is expanding at such a rapid pace that a veritable deluge of new knowledge and conjecture is descending on medical student and practitioner alike. In no field is this more true than in virology. However, many, overwhelmed by this inundation, are shrugging their shoulders in despair, unwilling to come to terms with this new and challenging discipline. It is to these people, as well as to those with an avid interest in virology, that this issue of the Medical Journal is directed, in the hope that it will provide the comprehensible and readily utilizable information they desire.

The science of virology has in the past brought forth discoveries of inestimable value in recognizing and combatting human disease. Vaccines against smallpox, poliomyelitis and yellow fever are examples that come readily to mind. However, future findings in this broad field will even more profoundly influence the professional activities of the internist, pediatrician, ophthalmologist, and immunologist. The problems facing them include the prevention and treatment of the exanthematous diseases of childhood, of infections of the respiratory tract (including the ubiquitous common cold), and of viral gastroenteritis and meningitis. These areas, and many others, will certainly provide a fertile field for investigation and a heady challenge to the virologist of tomorrow.

But what of the medical student of today? What material printed here would serve him best? It was with this consideration in mind that the articles on the following pages were chosen. "The Current Status of Diagnostic Virology" outlines the fundamentals of this field with emphasis on the specimens to be submitted to, and the procedures performed in, the viral laboratory. Although brief, this paper is remarkably comprehensive in scope and should, in the author's words, "encourage wider, more intelligent use of laboratory facilities available throughout Canada".

F. Simon, writing on the common cold, illustrates the difficulties encountered in isolating a virus and the problems of interpretation once isolation has been accomplished. The common cold is such a prevalent condition that our ignorance concerning it is apt to be underestimated; the author, in describing its aetiology, epidemiology, prevention, and treatment, has gone far toward remedying this deficiency.

The third paper, "Recent Advances in Antiviral Substances", presents experimental data culled from numerous articles, detailing the various chemicals that have been successfully employed in combatting viruses, both in tissue culture and *in vivo*. As well, the action of interferon and synthetic metabolic analogues is described and the clinical results of their use assessed. This is a complex topic but of such potential importance that it well merits the attention of the reader.

The remaining topics discussed in this journal are "Viral Diseases of the Nervous System" and "Infectious Hepatitis". The former summarizes current concepts of poliomyelitis, rabies, aseptic meningitis, and the encephalitides. The latter outlines recent advances in isolating the virus and clinical studies dealing with viral transmission in infectious hepatitis.

All the contributors to this issue have attempted to present their material in as pragmatic a manner as possible without obscuring the intrinsic interest of the subject matter *per se*. It is hoped that this will provide a sound background for following the many further developments that will arise in this field.

L.E.C.

EDITORIALS

Virology and malignancy, the topics of Issues 1 and 2 of this Journal, are moving into an ever closer relationship, as more sophisticated and detailed studies are done on the *oncogenic* viruses. In 1908 Ellerman and Bang first suggested this relationship when they transmitted the erythromyeloblastic form of chicken leukaemia by means of cell-free filtrates, and in 1911 Rous achieved cell-free transmission of a solid tumour, a spindle cell sarcoma of fowl.

While there seems to be little question that certain viruses do induce neoplastic change, the mechanisms of this carcinogenesis are still very much in doubt. The virus seems to act directly by inducing change from a normal to a malignant cell, rather than through a mechanism whereby a rare pre-existing cell grows more rapidly in a virus-infected environment. Certainly, a large number of cells are transformed when a large dose of Rous sarcoma virus is added to a culture of chick fibroblasts.

Neoplastic change, in the case of DNA viruses, may be the result of association of viral DNA with the cell chromosomes; new proteins could thus result, possessing new specificity and leading to changes in cell behaviour (as well as in virus multiplication). RNA viruses might act more directly, on the cellular messenger RNA, but how genetic changes might be passed on to daughter cells is unknown.

That viral multiplication is altered is shown by the failure to isolate virus from many virus-transformed cells. Efforts to show viral biological activity in such cells have been unsuccessful. However, recently Sjögren, Hellström, and Kell (1961) have detected a virus-specific cell antigen in polyoma-transformed cells, by showing that animals immunized against the polyoma virus are not susceptible to transplantation of virus-transformed cells. The transformed cells produced by "pure" Rous virus do not release virus with propagation; however, with exposure to either a virus termed *resistance-inducing factor* or Rous-associated virus, the transformed cells produce not only the "rescuing" virus, but also Rous virus.

Whether this viral DNA is present attached to cell chromosomes or free, as are bacterial episomes (see On Inspection), is unknown. If the latter were the case, the occasional loss of the virus during cell division, and reversion, might be expected, but this has never been observed. Nevertheless, this remains an area for investigation, as do the carcinogenic action of the RNA virus and the altered cell physiology (after viral infection) which is expressed as neoplastic change.

The viruses have been implicated, at least by *in vitro* and animal experimentation, as an etiological factor in carcinogenesis; perhaps some insight will be had into the same mechanism in the human with further study of the central African lymphoma (Burkitt tumour). This does not eliminate chemicals and physical agents, such as radiation, as important agents in carcinogenesis. Whether these will turn out to be independent etiological agents or predisposing factors in viral carcinogenesis remains to be seen.

B.E.K.

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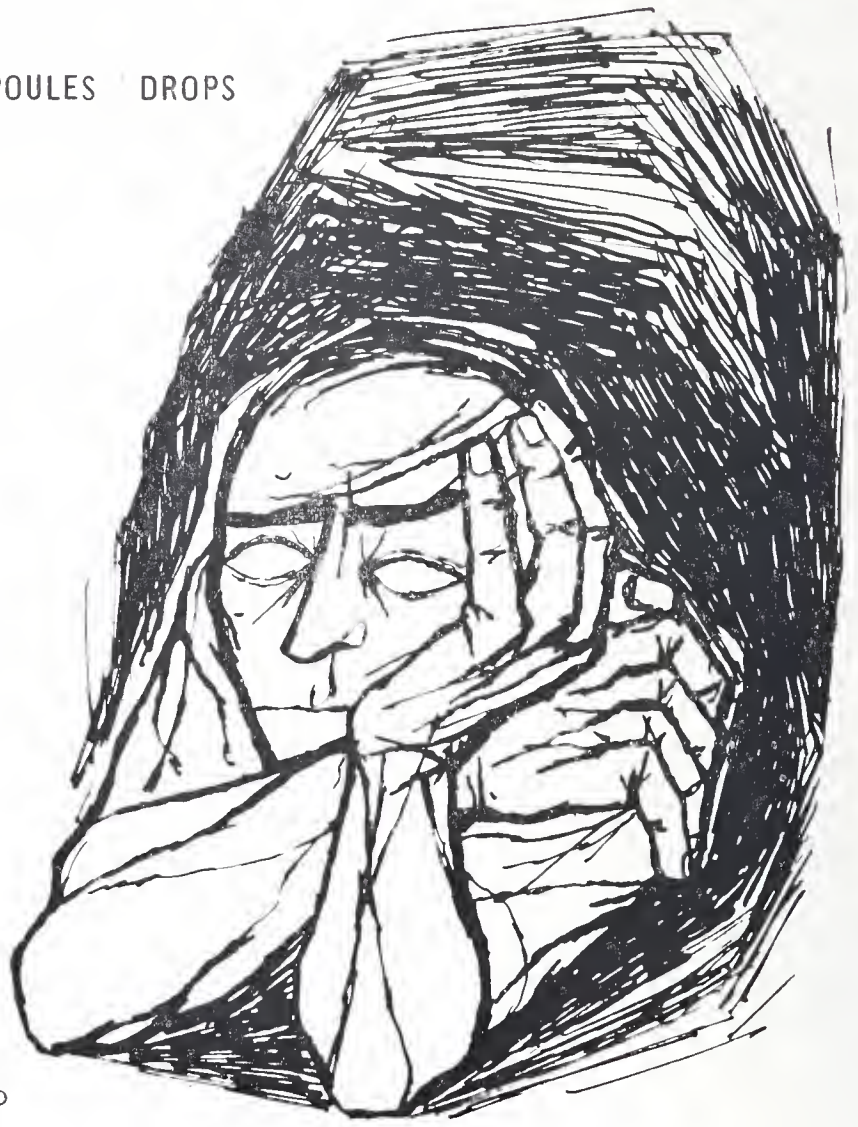

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The Current Status of Diagnostic Virology

R. P. B. Larke, M.D.*

Prior to 1960, there remained five human infections of presumed viral etiology (rubella, infectious hepatitis, serum hepatitis, the common cold and warts) from which a virus could not be isolated in the laboratory.[1] Today, the hepatitis viruses are the only agents which have not yet been isolated unequivocally.[2-5]

Interest in virology is steadily increasing amongst medical practitioners, due in part to the widespread use of live poliomyelitis and measles vaccines during the past few years. Unfortunately, the high cost of materials, shortage of qualified instructors and risk of accidental infection render training in virological techniques impractical at the medical school level. It is the purpose of this article to outline some fundamentals of diagnostic virology and to encourage wider, more intelligent use of laboratory facilities available throughout Canada.

CONTRIBUTIONS OF TISSUE CULTURE

Viruses grow only inside living cells and for many years virologists relied on embryonated eggs or mice and other small mammals for *in vivo* cultivation of viruses. A major advance came in 1949 when Enders, Weller and Robbins reported that poliovirus multiplied in non-neural human embryonic cells maintained in tissue culture, leading to characteristic degeneration of these cells.[6] Monolayer tissue cultures of monkey kidney cells are now widely used for diagnostic purposes. Epithelial cells are released from fragments of the renal cortex by the action of 0.25% trypsin, concentrated by centrifugation and suspended in nutrient medium. With incubation, a "monolayer" or sheet one cell in thickness grows out over the surface of bottles or tubes. This technique may be adapted to many other tissues of epithelial or fibroblastic origin such as human amnion and chick embryo.[7] These developments have been possible largely through the use of antibiotics added to reduce bacterial and fungal contamination which so impeded pioneer attempts at tissue culture.

In addition to such "primary" tissue cultures there are "continuous" or established lines of cells carried through many generations. The best known example of this type is the HeLa strain, derived from an epidermoid carcinoma of a patient in 1951.[8] Other lines, even those originated from normal tissue have eventually developed properties of malignant cells.

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With these tissue cultures available, new groups of human viruses such as ECHO viruses, adenoviruses and parainfluenza viruses were isolated during the period 1953 to 1958. In 1961, Hayflick and Moorhead reported the cultivation of human foetal tissues which, instead of taking on characteristics of malignant cells after serial propagation, retained properties of normal cells including the human diploid karyotype (46 chromosomes): however, they underwent degeneration after about 50 subcultivations.[9] As well as being sensitive to an extensive range of human viruses, including more than 50 types of rhinoviruses associated with the common cold, diploid cell strains have been shown thus far to be free from latent viruses which are a hazard, theoretically at least, in primary tissue cultures when they are used to propagate viruses for human vaccines.[10]

ROLE OF THE VIRUS DIAGNOSTIC LABORATORY

Clinical syndromes, including the "infectious diseases of childhood" can now be defined as to the precise etiological agent. The term "non-paralytic poliomyelitis" has given way to aseptic (or viral) meningitis, caused most frequently by a member of the ECHO or Coxsackie group of viruses or mumps, but only rarely by poliovirus. The clinical differentiation of various rashes, a problem faced particularly by the paediatrician, has now gained the attention of virologists. Five new exanthemata due to enteroviruses have been defined and are reviewed in two recent editorials.[11,12]

Using improved techniques, a specific diagnosis can often be made during the acute phase of an illness, permitting better management of patient and close contacts, more accurate prognosis and earlier recognition of subsequent cases in the community. Should smallpox or poliomyelitis be diagnosed, public health forces can be marshalled quickly to vaccinate poorly immunized populations; for example, in Dundee when widespread administration of trivalent living attenuated poliovirus vaccine (Sabin) was used successfully to halt a poliomyelitis outbreak in the summer of 1962.[13]

METHODS OF DIAGNOSIS

A. Direct Methods

1. Isolation of virus by inoculation of specimens into suitable tissue cultures, laboratory animals or embryonated eggs.

2. Microscopic examination of smears or scrapings (usually from skin or conjunctival lesions), appropriately stained to demonstrate virus elementary bodies or rickettsiae. Rabies may be diagnosed on finding Negri bodies in neuronal tissue of suspected cases, but in general, microscopic investigation is only ancillary to other methods.

Immunofluorescent techniques have been employed for early diagnosis of herpes, influenza, rabies and smallpox, but these techniques are highly specialized, and can be undertaken in relatively few laboratories.

B. Indirect Methods

1. Titration of antibody to a specific virus or group of viruses is performed on serum taken during acute and convalescent phases of illness in an attempt to demonsrate a rising antibody titre. Neutralization (NT), complement fixation (CF) and hemagglutination-inhibition (HI) tests are most commonly used. The latter measures antibody which specifically inhibits the agglutination that occurs when viruses such as mumps, vaccinia and influenza are added to a 1% suspension of erythrocytes from various species.

IDENTIFICATION OF VIRUSES BY DIRECT ISOLATION

A. In Tissue Culture

1. *Observation of cytopathic effect:* Many viruses cause necrosis or other changes in cells, generally termed "cytopathic effects". These are detected by microscopic examination of unstained monolayer cultures. The time of onset of cytopathic effect and the particular pattern of destruction often give some indication of the group of virus present.

2. *Interference:* Certain viruses multiply in tissue culture without causing obvious changes; however, their proliferation inhibits the growth and cytopathic effects produced by an unrelated enterovirus when the latter is added several days following inoculation of the first virus. This "interference technique" was used firstly for isolation of the rhinoviruses[4] and more recently for rubella virus.[2, 3]

3. *Hemadsorption:* Red blood cells of certain species will agglutinate on and adsorb to the surface of monolayers which are infected by viruses such as influenza, parainfluenza and mumps.

B. In Eggs

1. *Chorioallantoic membrane inoculation:* Smears and scrapings from lesions are extracted with 2 ml. of nutrient solution containing antibiotics and inoculated on the chorioallantoic membrane of 10-to 12-day-old fertile hens' eggs. Membranes are removed after two to three days' incubation at 37°C. and examined for the presence of characteristic lesions. For example, vaccinia pocks are 5 to 7 mm. diameter with hemorrhagic, ulcerated centres; those of alastrim (variola minor) and smallpox (variola major) are smaller (1 to 2 mm.) and non-hemmorrhagic. The last two may be differentiated by failure of alastrim virus to grow at 38.5°C. whereas variola major multiplies at that temperature.[14]

2. *Amniotic inoculation:* Throat washings or nasopharyngeal secretions from cases of respiratory illness are treated with antibiotics and inoculated into the amiotic cavities of 10-to 13-day-old embryonated eggs. Amniotic fluid is harvested after two to four days' incubation at 33° and 37°C; agglutination of a 1% suspension of guinea pig erythrocytes after addition to one drop of amniotic fluid indicates presence of a virus. This is most likely to be Influenza A or Influenza B virus, since other respiratory viruses such as parainfluenza viruses, reoviruses, adenoviruses and rhinoviruses do not multiply in eggs.

C. In Experimental Animals

Specimens of cerebrospinal fluid, blood, feces, organs removed at autopsy, or scrapings from skin lesions are freed of bacteria by centrifugation, or they are treated with antibiotics, before inoculation of weaned or suckling mice by the intracerebral or intraperitoneal routes. Depending on the type of virus, flaccid or spastic paralysis and/or encephalitis followed by death may occur one to seven days later. Exposure of the freshly isolated virus to ether or 1:1000 sodium deoxycholate will inactivate an arbovirus or herpes simplex, but Coxsackie viruses remain unaffected.

Typing Procedures

In order to identify a freshly isolated virus conclusively, one must first have certain possibilities in mind. The patient's history and clinical findings will frequently suggest at least the group of virus concerned. Characteristic cytopathic effects in various tissue cultures, or the appearance of lesions in eggs or animals give further clues. For example, a fecal extract from a child with fever, stiff neck and a fine macular rash may be inoculated into cultures or rhesus monkey kidney cells. Rounding up and death of these cells within two to five days suggests that the illness may be due to an enterovirus. Aliquots of the culture fluid containing the virus are then added to antisera prepared against several viruses known to cause such a syndrome and which may be prevalent in that community. The freshly isolated virus will be inactivated by antiserum to the same serotype, but not by antisera to heterologous viruses. Following incubation of cultures containing virus plus homotypic anti-serum no cytopathic effect will be observed upon microscopic examination, but tubes containing virus plus heterologous antisera will show cytopathic changes.

Myxoviruses such as influenza and parainfluenza may be typed more conveniently by complement fixation or hemagglutination inhibition tests using the virus isolate and various known antisera.

Interpretation of Results

Isolation of a virus from cerebrospinal fluid or brain obtained from conditions involving the central nervous system, or from skin lesions in the case of exanthemata is strong evidence that the virus caused the patient's disease, since these are sites of the essential pathological process. However, a virus isolated from feces or respiratory secretions, except in cases of influenza or other respirtaory tract infections should be considered as the etiological agent only when subsequent tests on acute and convalescent phase sera show a fourfold or greater rise in antibody titre to that particular virus.

No significance should be placed on a report from a single serum specimen taken at some random time during or after an illness. The presence of antibody in such a sample indicates solely that the patient has been infected with the particular virus at some time past.

SPECIMENS FOR VIRUS STUDIES

The virus diagnostic laboratory can provide most effective service if the following points are observed:

1. Collection of clinical or post-mortem material most likely to contain the virus;

2. Collection of such material as soon as possible after onset of illness.

3. Proper handling of materials once obtained.

In any illness of suspected viral etiology early consultation with a virologist will ensure proper selection and timing of specimens. If material must be shipped to a central laboratory, the clinician should seek direction from publications such as that issued by the Ontario Department of Health entitled "Viral and Rickettsial Infections—Notes on the Submission of Specimens".[15]

The sooner material reaches the laboratory for processing, the higher will be the virus isolation rate. In general, if the shipping period will exceed 24 hours, samples of serum, cerebrospinal fluid and throat washings should be forwarded in insulated containers containing ice cubes or dry ice. To avoid hemolysis, serum should always be separated from clot before freezing. Feces may be mailed without refrigeration in containers available through the respective Provincial Laboratories.

A brief history of the patient's illness plus any pertinent epidemiological data *must* accompany each specimen submitted for viral studies. Only with such information can the virologist choose tests which will most rapidly provide information helpful to the clinician.

The accompanying table summarizes the specimens to be submitted and the commonly used diagnostic tests for several disease categories frequently of viral etiology. A number of recent publications describe newer experimental techniques and give information on specific viral infections.[16 17 18]

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CLINICAL ENTITIES FOR WHICH VIRUS DIAGNOSTIC TESTS ARE AVAILABLE

(Adapted from McLean, et al., Canad. J. Public Health, 51:94, 1960.)

Clinical Group	Etiological Agents	Virus Isolation Tests		Microscopic Examination of Human Material		Serological Tests
		Specimens Submitted	Preferred Test System	Specimens Submitted	Characteristic Finding	
Central nervous system infections	Enterovirus	Cerebrospinal fluid, feces, throat swabs	Monkey kidney tissue culture	Brain sections	Neuronophagia, perivascular cuffing with lymphocytes	NT
	Myxovirus (mumps)	Cerebrospinal fluid, throat swab	Monkey kidney tissue culture Chick embryo (amniotic route)			HI, CF, NT
	Rabies	Brain, saliva	Suckling or weaned mice	Brain smear	Negri bodies Fluorescence	
	Arborvirus	Cerebrospinal fluid, blood, brain	Suckling mice, chick embryo fibroblast cultures	Brain sections	Neuronophagia, perivascular cuffing with lymphocytes	NT, CF, HI
Respiratory disease	Myxovirus (influenza, parainfluenza)	Throat washing or swab or nasopharyngeal suction	Monkey kidney tissue culture Chick embryo (amniotic route)			HI, NT, CF
	Respiratory syncytial	Throat washing or swab or nasopharyngeal suction	Hep-2, HeLa or monkey kidney tissue culture			NT, CF
	Adenovirus	Throat washing or swab or nasopharyngeal suction	HeLa or human amnion tissue culture			CF, NT
	Enterovirus and Reovirus	Throat washing or swab or nasopharyngeal suction	Monkey kidney or HeLa tissue culture			NT, CF, HI
	Rhinovirus°	Throat washing or swab or nasopharyngeal suction	Cultures of human embryonic tissue (Diploid lines)			NT, CF
	Psittacosis Ornithosis	Sputum	Chick embryo (yolk sac)			CF

° Tests for these viruses not readily available in routine diagnostic laboratories.

CF, Complement Fixation Test; HI, Hemagglutination Inhibition Test; NT, Neutralization Test.

Clinical Group	Etiological Agents	Virus Isolation Tests		Microscopic Examination of Human Material		Serological Tests
		Specimens Submitted	Preferred Test System	Specimens Submitted	Characteristic Finding	
Lesions of skin and mucous membranes						
A. Macular or Maculo-papular	Enterovirus	Throat swab, skin scraping, feces	Monkey kidney tissue culture, suckling mice			NT
	Rubella°	Throat swab or washing	Grivet monkey kidney tissue culture (for interference test)			NT
B. Vesicular	Herpesvirus	Scrapings from lesions	Suckling mice HeLa or human amnion tissue cultures	Scrapings of skin lesions brain sections	Giant cells; eosinophilic intranuclear inclusions	NT. CF
	Poxvirus	Scrapings or exudate from skin lesions; blood	Chick embryo (chorioallan-toic membrane)	Scrapings from skin lesions	Elementary bodies eosinophilic cytoplasmic inclusions (Guarnieri bodies)	HI. NT. CF
Eye diseases	Trachoma and inclusion blenorrhea	Conjunctival scrapings	Chick embryo (yolk sac)	Conjunctival scrapings	Basophilic cytoplasmic inclusions	CF
	Adenovirus	Conjunctival swab	HeLa or human amnion tissue cultures			CF. NT
Pleurodynia Pericarditis Myocarditis	Enterovirus	Feces, throat swab, serous effusions	Monkey kidney tissue culture	Heart	Pericarditis myocarditis	NT
Fevers due to arborviruses						
A. tropical zone	Yellow fever	Serum, liver	Suckling mice	Liver sections	Midzonal necrosis	NT. CF, HI
B. temperate zone	Colorado tick fever	Clotted blood	Suckling mice			NT. CF
Rickettsial diseases	Q-fever and Rocky Mountain spotted fever	Clotted blood	Male guinea pig, chick embryo (yolk sac)			CF, Weil-Felix agglutination

Medical Muses

Dr. Walter Reed

YELLOW FEVER

The discovery of the cause and transmission of yellow fever is a fascinating illustration of the courageous and brilliant work of medical scientists. Two men, Dr. Walter Reed and Dr. Carlos J. Finlay must be singled out for their contribution to the knowledge about yellow fever.

This disease is relatively 'new' for no history dates before Colombus' day. However, since that time, millions of people were reported as having died as a consequence of being infected. In the 18th and 19th centuries, losses in the hundreds of of thousands were recorded in United States. In 1802, Napoleon was forced to sell Louisiana because more than nine-tenths of his expeditionary force in San Domingo died with Yellow Fever.

Dr. Finlay's paper in 1881, "The Mosquito, Hypothetically Considered as the Agent of Transmission of Yellow Fever", was the first to incriminate the mosquito as the means of transmission and perpetuation of yellow fever. However, like many medical discoveries, his claims attracted little attention until Major Walter Reed, commissioned by the United States Army to study the mystery concerning the cause and transmission of this disease which was inflicting more losses among the United States Troops than the Spanish American War itself, came to Havana.

Dr. Reed was born in Virginia on September 13, 1851. He graduated from the Bellevue Hospital Medical College in New York in 1870. In 1875, he left his practice to enter the Army. After many years in the Western Frontier, he returned in 1889 to pursue further studies in the field of pathology and bacteriology at John Hopkins University. Soon he became curator of the Army Medical Museum and professor of bacteriology and clinical microscopy at the United States Army Medical School. At the turn of the 20th century, the Army commissioned Dr. Reed and Dr. Carroll to go to Havana to solve the yellow fever puzzle.

Unable to find a bacterial cause for the fever, Dr. Reed turned his attention to Dr. Finlay's theory of mosquito transmission and the prevailing medical theory that the disease was spread by personal contact and by the clothing, bedding and the personal effects of the sick.

To test these hypotheses, he established an experimental headquarters, Camp Lazear in Cuba. Two wooden structures were built. In one, volunteers lived for 20 days in poorly ventilated quarters containing the bedding, the excrement and the black vomitus of those who had died of the fever. In the other well ventilated cabin, which was divided into 2 sections by a screen, one group of volunteers allowed themselves to be bitten by mosquitoes while the other control group were protected from mosquitoes. Of the three different groups, only those who were bitten developed yellow fever. The results of the experiments at Camp Lazear clearly illustrated that the mosquito, Aedes aegypti, served as the intermediate host for the parasite of yellow fever, and transmitted the disease by its bite. Further, yellow fever was not conveyed by the contaminated articles of those afflicted with this disease.

With further experimental work, Dr. Carroll in 1901 proved that the causative agent was a filterable virus. However, it was not till some 30 years later that Dr. Max Theiler in the Rockefeller Foundation's Division of Biological and Medical Research in New York developed two strains of attenuated live yellow fever virus for possible use as vaccines. Till then, the only effective means of combatting this disease was extensive vigorous anti-mosquito campaigns.

Dr. Reed himself died suddenly in 1902 as a result of appendicitis. A tribute to his great work may be found in Washington, D.C. — the great Walter Reed Research Hospital.

A.G.L.

Abstract

Use of Water-Soluble Contrast Medium in Pediatric Radiology

Sidaway, M. E.: Clin. Radiol. 15: 132-138, Apr. 1964.

Barium remains the medium of choice for gastrointestinal examinations but gastrografin (an aqueous solution of the sodium methylglucamine salt of diatrizoic acid) has been used extensively. It is especially useful in examination of tracheo-oesophageal fistula, congenital esophageal stenosis and post-operative complications of these conditions since inhalation is much less harmful than inhalation of barium.

Gastrografin can be given safely by mouth for alimentary fistulae and intestinal obstruction if less than 5 mls are given. It is not helpful in pyloric stenosis since it leaves the stomach too quickly. After colostomy for anal atresia, gastrografin may be injected into the colostomy to outline the blind end of the rectum while barium may form a calculus, if used.

M.T.

The Common Cold

F. Simon 6T5

INTRODUCTION

The common cold is an ailment from which few have had the good fortune not to suffer, yet its etiology and the factors that influence susceptibility or resistance to infection have remained relatively obscure. Recently, however, with the aid of modern virological techniques, a group of new viruses known as rhinoviruses has been discovered and this promises to shed much light on the etiological aspects of the common cold.

The common cold is world-wide in distribution, although it is milder and less frequent in the tropics. Colds cause more lost time in industry than all other respiratory illnesses combined; according to a U.S. Public Health survey, about 2.2 days per person per year, which is almost 50 per cent of all absenteeism. The estimated loss of wages in the U.S. due to this one condition exceeds two billion dollars annually. Thus, the investigation of the etiology and prevention of the common cold is not only of great medical interest but is also of great economic importance.

ETIOLOGY

The common cold was originally thought to be due to bacterial infection. This error arose because bacteria are invariably found in nasal washings from those with colds. It was Kruse in 1914 who first produced colds in volunteers by the intranasal instillation of filtered nasal washings, showing that colds were caused by a filter-passing agent. His results were later confirmed by other investigators. However, progress in research on the common cold has been slow since it is impossible to infect a suitable experimental animal with the common cold and the chimpanzee is still the only animal known to be susceptible. This is the main reason that the Salisbury Common Cold Unit of the Medical Research Council of Great Britain was set up to study the transmission of the common cold in human volunteers by the intranasal inoculation of nasal secretions. Attempts to grow the virus of the common cold in the laboratory using egg media or human tissue culture proved unsuccessful. Finally, in 1960, Tyrrell and his colleagues were able to grow a virus by altering the conditions of tissue culture propagation of the virus. The basic conditions necessary are:

1. Trypsin-dispersed human embryo kidney cells must be used;
2. The cultures must be kept at 33°C;
3. They must be rotated during incubation;
4. The pH of the medium must be around 7.

Using these conditions the virus can be propagated in series indefinitely and a cytopathic effect is seen in the cultures.

Not all of the viruses so isolated from persons with upper respiratory tract infections are cold viruses and it is still necessary to inoculate them intranasally into volunteers to see whether or not they produce colds. Those that do are called rhinoviruses. Some of them will only grow in human embryo kidney, while others will grow in monkey kidney as well. These are referred to as H and M viruses respectively. However, there are a certain percentage of nasal washings which will produce colds in volunteers but from which a virus cannot be isolated. In a study by Kendall et al of common colds in a residential school in England viruses were isolated from only 30% of the colds, although all the nasal secretions could produce the cold syndrome when given to volunteers.

The rhinoviruses isolated in England belong to six serologically distinct types. Recent investigations in other laboratories report over twenty serologic types of rhinovirus and as techniques improve it seems quite probable that many more antigenically different strains will be distinguished.

Although it appears that the rhinovirus is associated with a larger proportion of common colds than any other group of virus, many other viruses are able to cause a common respiratory disease which is clinically indistinguishable from the common cold. Table 1 lists the principal viruses which cause a primary infection of the respiratory tract. Although these viruses commonly cause the clinical illness as listed they may produce a spectrum of respiratory illness which ranges from pneumonia to the common cold. Table 2 lists the viruses which are more likely to be associated with the common cold than with other forms of respiratory disease.

However, it is important to realize that every virus or other microorganism that can be cultured from the nasal or pharyngeal mucosa by specialized technique is not necessarily a cause of clinical respiratory disease. Many viral infections of the respiratory tract appear to be merely incidental and cause few, if any, symptoms. There are also many viruses which reproduce in the upper respiratory tract but are associated with major manifestations in other systems. (Table 3) The bulk of the data thus far accumulated supports the view that the rhinovirus is responsible for the majority of colds, but that any of the respiratory viruses listed in Table 1 can produce a clinical picture indistinguishable from the common cold.

TABLE 1

VIRUSES CAUSING PRIMARY INFECTIONS OF THE RESPIRATORY TRACT

VIRUS GROUP	MAJOR TYPES	COMMONEST CLINICAL ILLNESS
1. Measles	Measles virus	measles, croup
2. Myxovirus	Influenza A	influenza
	" B	"
	" C	"
	Mumps	mumps, encephalitis
	Parainfluenza 1, 2, 3, 4	mild resp. diseases, croup
3. Adenovirus	Types 2, 4, 7, 7a	acute U.R.I., epidemic keratoconjunctivitis
4. Reovirus	Types 1, 2, 3	acute U.R.I.
5. Rhinovirus	over 30 types	common cold
6. Enterovirus	E.C.H.O. (6, 11, 20, 28*)	U.R.I.
	Coxsackie A21 (Coe)	common cold
7. Miscellaneous	Eaton agent	viral pneumonia
	Resp. Syncytial Virus	minor U.R.I., colds, croup
8. Basophilic V.	Psittacosis	pneumonia
	Ornithosis	pneumonia

TABLE 2

VIRUSES ASSOCIATED WITH THE COMMON COLD

VIRUS	TYPE OF ILLNESS
1. Coe	Colds or febrile illness of resp. tract in recruits
2. Parainfluenza	1. Febrile resp. disease in children, colds in adults 2. Croup in children, colds in adults 3. Febrile resp. disease in children, colds in adults 4. Colds in adults
3. Resp. Syncytial Virus	Febrile resp. disease (especially bronchiolitis) in children, colds in adults
4. Rhinovirus gp.	Colds in adults and children
5. ECHO 28 (JH2060)	Colds in adults and children

TABLE 3

RESPIRATORY VIRUSES ASSOCIATED WITH MAJOR MANIFESTATIONS IN OTHER SYSTEMS

VIRUS	CLINICAL MANIFESTATIONS
Herpes simplex	fever blisters, encephalitis, keratitis
Varicella	chicken pox, Herpes zoster
Variola	small pox
Rubeola	measles
Myxovirus mumps	parotitis, orchitis, encephalitis
Enterovirus gp.	
polio	meningitis, paralysis
coxsackie A	meningitis, rash, febrile illness, herpangina
B	meningitis, pleurodynia
ECHO	meningitis, rash, diarrhea

EPIDEMIOLOGY

The clinical illness known as the common cold is mainly a subjective one with a particular symptom complex. It is most frequently described as an afebrile, mild upper respiratory infection characterized chiefly by rhinitis with or without pharyngitis. The kind of symptomatic illness produced may be related to the age of the person or to any previous infection with the same or related organism. In this context the common cold might be the clinical manifestation of a certain infection in an adult, especially one with some serum antibodies, whereas the same infection among children can produce a severe respiratory disease. This phenomenon has been shown by the administration of respiratory syncytial virus to volunteers who had specific antibody against the virus in their serum, compared to the natural infection observed among children and unprotected adults. Other factors which affect the clinical picture include previous inapparent infections with the same or related virus, the changing prevalence of viruses, the concentrations of the virus required to cause symptoms, its state of attenuation and the host's previous experience with it.

The extreme diversity of serotypes among rhinoviruses goes far toward explaining the reccurrent nature of the cold and emphasizes the likely difficulty in development of an effective vaccine. When an individual acquires infection with one serotype of rhinovirus, some immunity does result against that particular serotype but the person can still become infected with any of the other 29 serotypes. Serological studies show that three to four weeks after the initial illness protective antibody in the serum is negligible and susceptibility to rechallenge with the same virus is reduced only 40 per cent. By three to four months after a common cold, immunity to reinfection with the same virus is almost complete and convalescent serum collected after six months is highly affective in neutralizing the virus. The protective capacity of the serum begins to decline after 18 months, and by two years after the initial infection the titre has declined sufficiently to suggest that reinfection is likely. However, clinically, the relationship between antibody levels and effective immunity to reinfection with the same virus is not clearly defined.

The incidence of colds in adults varies greatly, from none at all to seven or more a year. It is higher in children and in those living in overcrowded and insanitary dwellings. Colds are spread by personal contact and transmission is believed to occur by the inhalation of infected droplets. Droplets are more infectious during the early phase of a cold than in the convalescent period. Experimental colds are usually produced by dropping the infected secretions up the nose but they have also been produced by swabbing the conjunctiva. No colds occurred if the virus was given by intramuscular injection.

The reasons for the increased incidence of colds in the winter are still uncertain. Low temperature itself does not appear to be a cause, as shown by the low incidence of colds among inhabitants of the arctic island of Spitzbergen and the frequency of colds among the inhabitants of tropical islands. Experimenters employing volunteers were unable to produce the common cold among uninfected subjects by mere chilling. Also, volunteers who were chilled were no more susceptible to challenge with an infectious secretion than others who had no exposure to cold. This was true even when the temperature of the nasal turbinates dropped to a level of 30°-33°C., which is the temperature which favours the growth of the rhinovirus in tissue culture. The accumulated evidence suggests that the observed relation between season and respiratory ilness is more likely a consequence of changes in the pattern of personal activities than to the effect of climatic cold. This is evidenced by the increased indoor activity during the winter months and the resultant close confinement in schools, offices, and social gatherings.

As with any infectious disease, host factors are important in the manifestations of infection with the common cold viruses. One group of people appears to be naturally quite resistant to infection whereas another group is very susceptible: the majority fall somewhere in between. After challenge with an infectious secretion the naturally resistant group had significantly fewer colds. Among the subjects with an increased natural susceptibility, colds developed almost as frequently following the instillation of noninfectious material as with infectious secretions. Thus, the perennial "cold getter" probably has no more viral colds than the average but he develops similar nasopharyngeal symptoms from noninfectious stimuli. The "non-cold getter" seems to have a natural resistance against a symptomatic response to infection, although the actual number of viral respiratory infections is no less than that acquired by others. There was no significant difference in the antibody titres between these two groups.

It has been observed that people with a history of allergy are more susceptible to a symptomatic response after being challenged with an infectious secretion. Challenge with a non-infectious material, however, did not cause significantly more colds in the group without. Thus, an individual's response to a viral infection will vary both according to his natural susceptibilities as well as to his previous experiences.

The resistance to infection with the cold viruses which certain people exhibit may be related to an intrinsically reduced ability of their cells to support viral growth. Those of blood group O are more likely to be admitted to hospital with an illness due to Influenza AS than those of blood group A; the reverse is true of illness due to adenovirus. This may be due to a genetically determined tendency by which the cells are either less able to support viral growth or the body is more capable of producing antiviral substances against that particular viral strain. However, the multiplicity of factors

which help to determine one's natural susceptibility or resistance to viral infections have yet to be clearly defined.

PREVENTION AND TREATMENT

1. Vaccines

The prospect of an effective vaccine to control the common cold in the near future is not very bright. The task of formulating such a vaccine is enormous because of the number of viruses which are candidates for inclusion. Obviously the rhinoviruses would be an important component of any vaccine prepared to prevent the cold in young adults. When more information is available concerning the etiological agents of the common cold in different areas, it may be possible to select certain strains of rhinovirus as the most common and include these in a vaccine. The relative success in preparing an effective vaccine against certain strains of influenza virus enables one to be optimistic of a similar outcome with prevalent strains of common cold virus.

2. Antiviral Agents

The possibility of producing an antivoral drug is receiving much attention but, since viruses are made up of the same chemical constituents as their hosts, the problem is to find an agent which will inhibit viral growth without damaging the host cells. Intensive research to this end is now being carried out. The only antiviral agent which is now available for therapeutic purposes is IDU (5-iodo -2'-deoxyuridine). It is very useful in treating keratitis caused by herpes simplex virus and in vaccinia. It appears that this agent acts either on the terminal virus-specific stages of DNA synthesis or on the assembly of the virus. It seems likely that any other antiviral agent, in order to be effective, must also act at either of these stages.

An alternative to an antiviral drug is the interferons. The interferons are non-viral proteins produced by virus infected cells but not by normal cells. They inhibit virus reproduction by their action on cells, not by attacking the invading virus directly. There is evidence to suggest that interferon synthesis is directly controlled by cellular nucleic acid and that the virus merely acts as an inducing agent or irritant. It seems likely that most cells "know" how to make interferon but can do so only in response to viral infection; proof of this would lend credence to the proposition that interferon production is a specific cellular mechanism for defence against the intrusion of foreign viral nucleic acid into a cell.

Interferon appears early, long before antibody is produced and it seems to play the major role in overcoming an initial viral infection while antibody is being produced to protect against reinfection. It is active against the rhinovirus and, hence, might prove beneficial in the treatment of the common cold. However, interferon production is specific and it cannot be manufactured in sufficient quantity at the present to be of therapeutic importance. The continuing research into its mechanism of action may lead to the discovery of other, more potent antiviral agents.

3. Antibiotics

Antibiotics are not indicated in the treatment of the common cold except to combat any bacterial complications when they occur. They are of use of treat bronchitis or other chronic respiratory diseases that may be made worse because of the viral invasion of already infected tissues. Antibiotics are also af value in children with fibrinocystic disease. They should not be used indiscriminately and when used should be given in full therapeutic dosage to prevent the production of resistant organisms.

4. Symptomatic Treatment

There is at present no specific treatment for the common cold and all our present measures are directed towards alleviating the symptoms. Aspirin is the most popular remedy and is as good as any for the relief of malaise, fever, and headaches. The antihistamines are of little value in colds of true viral origin but may help to relieve the symtoms of allergy which may be present in conjunction with a cold. Nasal decongestants may be of value to open up a blocked passage but they should not be used for prolonged periods since excessive or continued use may cause irritation and rebound congestion. Warm, moist heat may also prove helpful. The popular household panaceas of hot lemonade, vitamins, a shot of whisky, etc. do not appear to have any effect on the natural course of the disease. Of all these remedies the latter has perhaps the most to offer; although it may not alter the course of the disease, it makes the symptoms more tolerable.

SUMMARY

The implication of many different viruses in the etiology of the cold syndrome is discussed. The effects of this, plus environmental factors, make this syndrome a complex one. The immunologic factors involved are just beginning to be investigated. Therapy is, in the main, symptomatic.

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Recent Advances In Antiviral Substances

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INTRODUCTION

Research in virology is progressing at an astounding pace. The search for antiviral chemicals has resulted in the discovery of many products. Some of these so far have been effective in tissue culture and await experimental trials in animals and later in the clinics. Others have been successful *in vivo,* on experimental animals. but have not yet been administered to man. Only very few clinical trials have been reported in the literature. They involved interferon, synthetic metabolic analogues (like I.D.U., Marboran, Virugon) and some mould products. Attention in this review has been mainly devoted to these substances, but the long list of other compounds successful in viral inhibition should urge every clinician to consider them in clinical experiments.

ANTIVIRAL SUBSTANCES

ANTIVIRAL SUBSTANCES BASED ON ANIMAL EXPERIMENTS (*in vivo*)	VIRUSES INHIBITED	ANIMAL
1. Xerosin	influenza A, B	Mouse
2. Darvisul	polio	,,
3. Netropsin	vaccinia	,,
4. Helenin	polio, influenza, EMC, semiliki forest virus	,,
5. antiviral agent 8450	semiliki forest virus	
	polio	,,
6. capsular polysaccaride of klebsiella	influenza B	
	mumps	,,
7. proponibacterium product	Cel-SK-virus	,,
8. abalone juice	polio I, II	,,
9. mollusc extract	polio, influenza	,,
10. thymus water extract	polio 1, Cox A 9	,,
11. pyridine nucleoside	herpes keratitis	rabbit
12. cyclopin	WEE, sindbitz, W N. chikungunya, echo II, polio 1, H. Simplex adeno-2. Cox A 9, Cox-B2	monkey

These have yet to be tried out clinically.

ANTIVIRAL SUBSTANCES BASED ON TISSUE CULTURE STUDIES	VIRUSES INHIBITED
1. aureomycin	Rous sarcoma virus, psittacosis, meningo-pneumonitis
2. tetracycline	Eaton agent, trachoma
3. oxytetracycline	trachoma, psittacosis
4. terramycin	Rous sarcoma virus
5. chlortetracycline	trachoma
6. streptomycin	Eaton agent
7. neomycin	Rous sarcoma virus
8. penicillin	trachoma
9. chloramphenicol	trachoma
10. erythromycin	trachoma
11. sulfa-diazine	psittacosis
12. sulfonilamide-3-phenyl-2-pyrazol	trachoma
13. di-phenyl-sulphones	H. Simplex, H. Zoster
14. sulfoniazide	polio, vaccinia
15. actinomycin D	Rous sarcoma virus, vaccinia
16. mitomycin	vaccinia
17. puromycin	N D V
18. statolon	Cox-A 21
19. antibiotic PA-96	Rous sarcoma virus
20. antiviral agent 1758	polio
21. benzimidazole	enteroviruses
22. aminopterin	trachoma
23. N-ethyl-beta-thio-semi-carbazone	alastrium
24. female genital tract excretion	H. Simplex, polio. Rous sarcoma virus
25. glucoxal derivatives	influenza, polio
26. urea derivatives	influenza, polio
27. acridine derivatives	polio, vaccinia, mumps, equinal encephalitis, influenza
28. tenuazonic acid	measles, Cox-B, vaccinia, polio II, parainfluenza, echo 9, H. Simplex

I. INTERFERON

Interferon is a protein, stable at a pH of 2, with a molecular weight of 70,000. In the presence of interferon chick embryo cells showed an increased aerobic

glycolysis, an increased uptake of inorganic phosphate and a decreased oxidation of glucose. It is produced by the action of living or inactivated viruses on cells, especially under slightly acidic conditions. Formation of interferon is shown to be the cells' response to foreign nucleic acid contributed by a virus. The cellular specificity of interferon depends on the tissue it was prepared in. When prepared in homologous species of cells, it has the greatest effects, but significant inhibition was also produced by some interferons prepared from heterologous cells. Virulent viruses seem to be poor initiators of interferon production and they are relatively insensitive to its antiviral action. There is a close relation between the onset of recovery and the appearance of interferon in the serum. When viruses are intravenously injected into an animal, interferon may be detected in the serum within an hour. The maximum level is reached in four hours. Rapidly produced interferon may play a role in the fast neutralization of the foreign virus.

Experiments suggest that interferon inhibits some early stage of virus synthesis. Action occurs within the cell after penetration of virus and before formation of mature virus particles. There is a close relation to viral RNA metabolism. Interferon does not block intracellular sites of attachment for viral multiplication nor does its effect depend upon direct inactivation of parental viral R.N.A., but it seems to inhibit the synthesis of messenger R.N.A. The inhibition of viral growth occurs under both aerobic and anaerobic conditions.

Interferon-like substances may be liberated by leucocytes *in vivo* after infection with some viruses. The local acid production in inflamed areas is favourable for interferon activity and may function as a homeostatic mechanism limiting virus growth.

Uncoupling agents like dinitrophenol, sodium azide, dicumarol and janus green, when given at doses that inhibit virus multiplication, also inhibit the production of interferon by ultraviolet irradiated virus. Trypsin, fluoro-phenyl-alanine and a high pH interfere with interferon activity. Cortisone inhibits the synthesis and action of interferon. It seems possible that endogenous adrenal corticoids may influence the dynamics and outcome of infection *in vivo* depending on the balance of their effects upon viral synthesis and on the synthesis and action of interferon. Conversely, under certain conditions the presence of the hormone enhances the viral inhibitory activity of the interferon, the effect being most pronounced with dianabol. The inhibition and enhancement suggest a double mechanism of steroidal activity. Polynuclear hydrocarbons (carcinogens) inhibit interferon formation. Hence, it is conceivable that the administration of such chemicals to oncogenic virus carriers could prompt and aggravate the induction of tumors by activating a hitherto latent virus. Animals exposed to increased oxygen tension suffer more severely from viral infections than those under normal oxygen tension due to decreased antiviral action of interferon. Therefore, the wisdom of routinely treating viral infections of the respiratory tract in infants by placing them into oxygen tents may be questionable.

When a virus enters a cell, it may take one of two paths. It may switch off the production of interferon and multiply, or it may do the opposite and not multiply. Temperature may be an important factor in deciding which pathway is followed. For many viruses the optimal temperature for producing interferon is higher than the optimal temperature at which virus plaques are formed. The poor growth of virus which occurs at supraoptimal temperature could be due to the fact that under these conditions the production of interferon is favoured. Viruses with low optimal temperature for growth were more sensitive for the antiviral action of interferon and generally produced higher yields of interferon than viruses with a high optimal temperature for growth.

Interferon has a broad antiviral spectrum embracing entero-, influenza, encephalitis, pox, arbor, common cold and measles viruses. The main obstacle to its widespread use is the difficulty of manufacturing large quantities by a biological process. There is a possibility that interferon may be used to treat superficial viral lesions by early topical application to prevent the spread of virus to neighboring epithelial cells of eye or skin. In one clinical trial five cases of vaccinial keratitis were treated with monkey interferon which was applied for half an hour during waking hours. In all cases the granular opacification of the epithelium resolved within a day. In all cases, whether treated by interferon or debridement, the epithelial keratitis was followed by stromal edema and diffuse infiltration. As this receded, punctuate superficial stromal opacity appeared, usually in a ring 5-6 mm. in diameter. Thus, the anti-viral effect on epithelial keratitis is striking but stromal sequelae ensue in spite of interferon.

In addition, a highly significant degree of protection was observed in thirty-eight volunteers vaccinated against smallpox. They had been injected at one site with interferon and at another with control fluid. Next day they were vaccinated at each site with two closely spaced scratches. A small drop of vaccine lymph was rubbed into the scratched areas. Only 50% showed infection of the interferon site. All control sites were infected. Here, for the first time, a rough measure of the potency of interferon required to produce a detectable antiviral action in man was obtained.

II. SYNTHETIC METABOLIC ANALOGUES

1. *IDU (5-iodo-2-desoxy-uridine)* (Trade names — Kerecid and Stoxil)

IDU inhibits the DNA formation by competing with the naturally occurring thymidine in viral DNA. It is not effective against RNA virses and too toxic for systemic use. Indications are H. Simplex infections of the cornea, especially when limited to the corneal epithelium, H. Simplex of the skin, and possibly vac-

cinial keratitis. Most uncomplicated dendritic ulcers will heal in 3-5 days, but in stromal herpes, when the disease extends deeper than the epithelial layers of the cornea, results are less satisfactory. A combination of steroids and IDU may help but use should be cautious. Uncomplicated ulcers are treated by one drop of IDU into the eye every hour of the day and every 2 hours of the night. When superficial lesions are healed, dosage can be reduced to one drop every 2 hours of the day and every 4 hours of the night. Side effects include occasional irritation, inflammation and edema of the eye or lid. Prolonged administration may damage the cornea, even to the extent of perforation of the cornea.

One clinical trial involved 9 cases of dendritic ulceration, with 8 of these clearing in 3-5 days after 2 hourly installations of 1% IDU. Cases of longer standing took longer to heal. Patients with superficial punctuate keratitis, however, showed no response to the treatment. Herpetic iritis, bullous keratopathy or disciform lesions with folds in the Descemet's membrane were benefitted by a combination of IDU and corticosteroids which, by suppression of inflammation and scar formation, were vision saving. There was also a dramatic response in 6 cases of trigeminal H. Zoster. The erythema settled in 48 hours, bullae dried in 72 hours and dark crusts formed that separated in a week.

Some investigators reported gradual virus resistance to treatment by IDU, analogous to that of staphylococci to penicillin. There is hope that cytosine arainoside may control such viruses.

2. *MARBORAN (N-methyl-isatin-B-thiosemicarbazone)*

Also known as compound 33T 57, this product is manufactured by the Wellcome Laboratories of Tropical Medicine in London. In India a Marboran-treated group of smallpox contacts who had never been vaccinated before showed a 96% reduction of outbreaks. Another study reevaled that eczema vaccinatum could be dramatically improved after the third day when Marboran was given to a six year old at doses of 250 mgm every six hours. Furthermore, vaccinia gangrenosa could be treated by giving 5 g/day of Marboran for 7 days. No significant effect on the clinical course of Herpes genitalia or H. Simplex was recorded when 6 patients received Marboran orally at doses of 1 g. 3 times a day for 2 days. Side effects including vomiting, and were overcome by cyclizine.

3. *VIRUGON (N',N-anhydrobis (B-hydroxy-ethyl) biguanide HCL) (Flumidin, ABOB)*

This product has some value in dermatology, where cases of acrodermatitis, H. Zoster, H. Simplex and aphthosis were effectively treated. However, several clinical tests could not substantiate previous claims of effectiveness against mumps, measles, varicella and upper respiratory infections.

III. MISCELLANEOUS COMPOUNDS

Clinical tests indicate that influenza, herpes and common cold viruses are destroyed by alpha-oxo-di-phenyl- beta -(phenyl - di - methyl-pyrazolone) amino ethane. At the outbreak of influenza B., students received 10 mg./Kg/day for 8 weeks of 1,1 - (3 - oxa - pentamethyline) biguanide: this suppressed the disease without having toxic effects.

IV. OTHER VIRUS DISEASES THAT HAVE BEEN SUCCESSFULLY TREATED

a) *Warts*

Chloroquin or hydrochloroquin destroy warts in an average of seven weeks. Recent warts, plain warts and children's lesions respond best. 166 of 258 patients achieved disappearance of all warts. In 37 patients gastrointestinal disturbance, weight loss, skin rash, visual disturbance or bleached hair resulted.

b) *Primary Atypical Pneumonia*

A prompt therapeutic response was obtained with declomycin which reduced fever, rales, cough, malaise and fatigue. In addition, treatment accelerated the clearing of the pulmonary infiltration. The dose was 0.9 gm/day for 6 days. Cold agglutinins were demonstrated in the serum of patients after the middle of the second week of the disease.

c) *Psittacosis and Lymphogranuloma Venereum*

After a 12 day course of treatment with aureomycin, 1 gm daily, a psittacosis patient had a relapse, but responded well to a second course of treatment in which up to 3 gm daily were used. 10 patients with lymphogranuloma venereum received sulfa-methoxypyridazine therapy after which pain and tenderness over bubos subsided in 48-72 hours. The rash and fever of one patient responded in 48 hours.

d) *Trachoma*

24 cases were given a mass treatment with 2.5 g. acetylsulfa-methopyrazine intramuscularly and 1.5 gm sulfamethopyrazine orally. Others were treated with 1% tetracycline in oil or ointment administered topically 4 times daily for 6 weeks. A third group was given a 2/3 standard daily dosage of sulfonamide for 3 weeks. All improved. Inclusion blennorrhoea has been treated similarly with some success.

CONCLUSION

Specific antiviral treatment is still entirely experimental but the multiplicity of antiviral agents allows a wide range of clinical studies. The approach may involve varying the doses of the substances or combining them in an effort to destroy the virus. Parallel studies may also be done, using one substance in one group of subjects and another substance in another group. The important thing is to act and to utilize some of the specific substances that have worked in the laboratories.

ACKNOWLEDGMENT

Dr. Franklin of the bacteriology department at the University of Toronto has compiled a set of excerpts from several hundred articles discussing antiviral substances. These appeared in the scientific literature during the past four years. I am greatly indebted to Dr. Franklin for the use of his notes, for valuable suggestions and encouragement in the preparation of this article.

Book Review

SIGNS AND SYMPTOMS: Applied Pathologic Physiology and Clinical Interpretation.

4th Ed. C. M. MacBryde (Ed). 971 pp. Illust. J. B. Lippincott Co., Philadelphia & Montreal, 1964. $15.00

In the Preface to the First Edition the editor of this book proposes to provide "the basis for analysis and interpretation of some of the commonest symptoms which bring patients to the doctor". His hope is that the material presented will permit a more meaningful history to obtained and a more skilful utilization of laboratory aids.

The topics discussed in most instances carry out the editor's intent. He covers many of the basic signs and symptoms encountered in medicine, first of all stating actual or posited mechanisms, with extensive references to experimental work; then, the manifestations of these signs and symptoms in various disease states are discussed, with an effort to illustrate the differing manners of presentation.

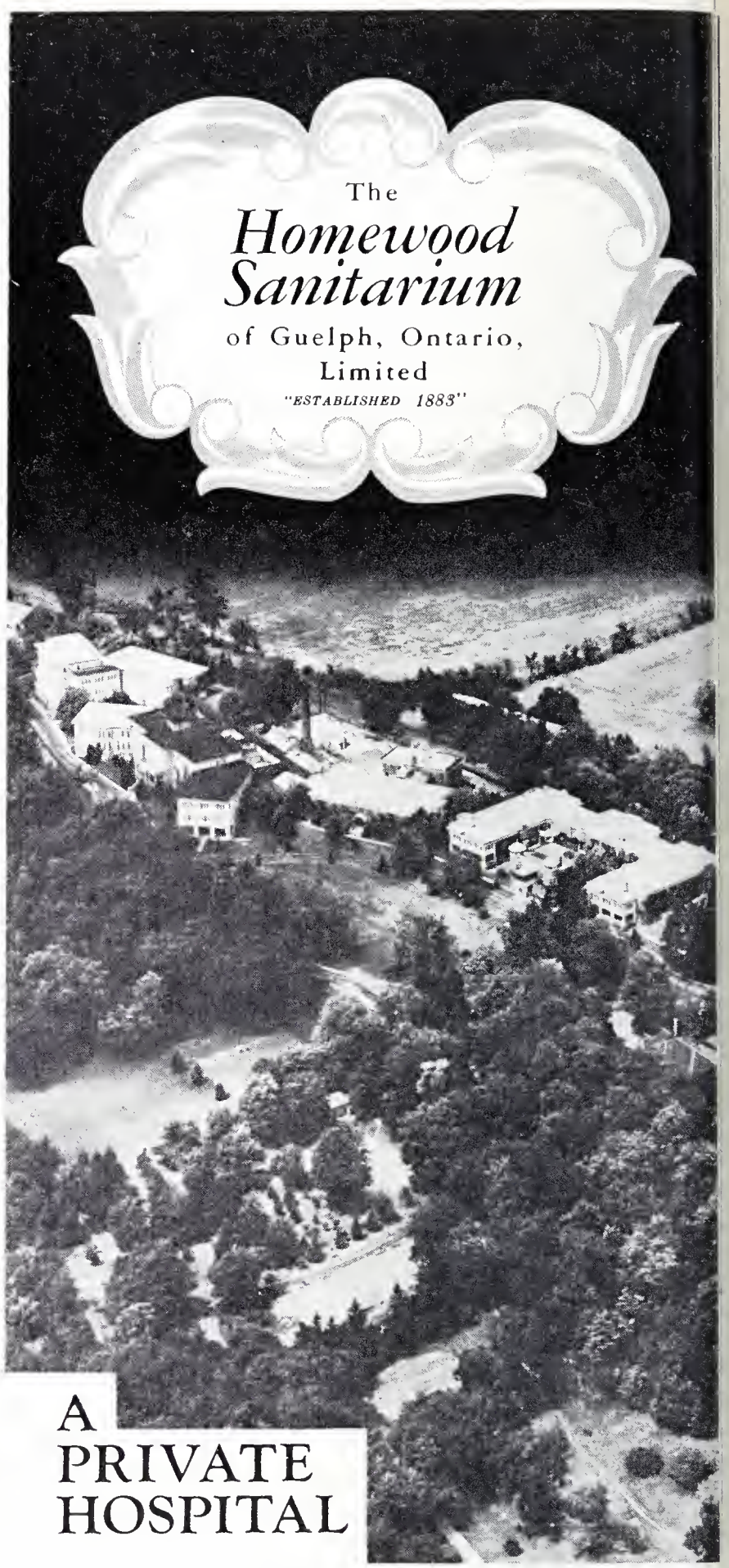
Almost 200 pages are devoted to an intensive and thorough discussion of pain, including a chapter on sore tongue and mouth, a symptom of which the differential diagnosis confuses many physicians. Other valuable chapters are those on dyspnea, fever, lymphadenopathy and disorders of the lymphatic system, and pathologic bleeding. However, certain topics might well have been deleted, for they receive such a superficial coverage as to be of little value; in particular, the chapters on generalized vasospasm and hypertension and on dehydration, fluid and electrolyte imbalances.

The employment of specific reference numbers is a feature which other texts might well emulate.

Organization is a crucial factor in a text such as this, and, in general, is competent. An exception is the chapter on growth and development, which meanders.

This book offers a fine survey of the mechanisms and presentations of many of the common signs and symptoms of clinical medicine. In most textbooks of general medicine these are assumed to be understood, thereby leaving gaps in the student's knowledge. Signs and Symptoms fills in many such gaps. While its price will deter most students from buying, its content makes it a worthwhile reference to be consulted in the library.

B.E.K.



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Virus Infections of the Nervous System

B. W. Pearson 6T6

Many viruses can produce disease in the nervous system. The frequency and severity of neurologic involvement varies widely with different strains of viruses. Diagnosis may be obvious when the neurological manifestations appear during a recognized disease known to carry risk of neurological complications, such as mumps or chickenpox. When the signs of organ involvement are confined to the nervous system, identification of the causative virus can be a laborious procedure, and the laboratories commonly fail to establish the etiology of 30-50% of cases.[1]

In spite of the large number of viruses which can attack the nervous system *only three major syndromes are regularly seen:*[2]

(i) *Poliomyelitis* syndrome (prodromal *fever* which is followed by *relapse* of fever, signs of meningeal irritation and muscle *paresis and paralysis* without sensory involvement);

(ii) The syndrome of *encephalitis or meningoencephalitis* (acute febrile illness with signs of meningeal irritation, stupor, confusion, *motor, sensory* and co-ordination defects);

(iii) The syndrome of *aseptic meningitis* (fever, signs of severe meningeal irritation and a distinctly *abnormal cerebrospinal fluid* persisting throughout the course of the illness).

Several disorders amenable to specific therapy; for example, tuberculosis; can produce these syndromes, so it is important to pursue the diagnosis bearing in mind the non-viral, as well as the viral, etiologies. When the cause is a virus, identification is often not achieved until the patient is convalescent. Nevertheless, the information is essential for prognosis, epidemiologic studies and for planning prophylactic programmes. Diagnosis is delayed because we are dependent on the laboratory results for specific identification of the etiological agent. The lab attempts to grow viruses from the submitted specimens, (i.e., faeces, C.S.F., swabs, etc.); the viruses are subsequently identified by observing the *disease* produced in laboratory animals or the *cytopathogenic effects* and *sero-reactions* of the virus in tissue culture and on chick egg membranes. Frequently no virus is isolated and the diagnosis rests on the demonstration of a *rise in titre* of an antiviral antibody in the patient's blood. For this purpose paired sera, acute and convalescent, must be submitted, again making for a late diagnosis.[3]

VIRAL ENCEPHALITIS

Definition of Terms

Encephalitis means inflammation of the brain which can be caused by many recognized agents; for example, chemical, bacterial, viral. *Viral encephalitis* denotes an etiology but the pathology remains non-specific. *Encephalomyelitis* includes conditions with spinal cord involvement which may be primary or secondary.

Etiology

The following classification groups the causative factors in two different manners. In the first we divide the recognized diseases into those of known and those of suspected viral etiology, and, under known, those caused by arbor viruses which are specific for the nervous system; i.e., neurotropic (when they occur in man) and those caused by viruses which are viscerotropic.[4]

I *Known Viral Etiology*

(a) *Arbor*

Eastern equine encephalitis, Venezuelan equine encephalitis, Western equine encephalitis, Japanese B encephalitis, louping ill, Murray Valley encephalitis, Russian spring-summer encephalitis (Russian S.S.E.), St. Louis encephalitis.

(b) *Other*

Coxsackie, ECHO (Enteric Cytopathogenic Human Orphan), encephalomyocarditis, *herpes simplex* (HS), herpes zoster (HZ), infectious mononucleosis (IM), lymphocytic choriomeningitis (LCM), lymphogranuloma venereum, *measles, mumps*, polio, rabies, Sabin B virus, *varicella*.

II *Possible Viral Etiology*

(Immune reactions precipitated by viral infections.)

(a) *Demyelinating* Acute haemorrhagic encephalitis, multiple sclerosis (MS), post-infectious and post-vaccinal encephalitides.

(b) *Non-Demyelinating* von Economo's disease, Guillain-Barre syndrome.

The second classification[5] is based on the manner of presentation of the encephalitis and is, perhaps, more useful from the diagnostician's standpoint.

I *Epidemic*

(a) *Enteric* Polio, ECHO, Coxsackie.
(b) *Arbor*
(c) *von Economo's*

II *Sporadic*

Rabies, lymphocytic choriomeningitis, HS, HZ, mumps.

III *Post-infectious*

Measles, rubella, varicella, IM, those following non-specific respiratory infections.

IV *Post-Vaccinal*

Vaccinia, rabies.

In I and II the neuronal damage and inflammation results from direct involvement of the nervous tissue by the virus, while in III and IV a different mechanism, probably some form of hypersensitivity, is involved.

Clinical Manifestations

The clinical syndrome of encephalitis consists of an acute febrile illness with meningeal symptoms to which are added various combinations of stupor, confusion, hallucinations, coma, hemiparesis, sensory changes, pathologic reflexes, tremor, ataxia, and disordered ocular movements. Death occurs in 5-20% of patients with viral encephalitis. Residual signs, such as mental deterioration, amnesic defect, personality change and paresis, usually spastic, are seen in about twenty per cent of trose who recover. However, there is wide variability in the prognosis depending on the agent. For example, residual defects occur in 80-90% of Eastern equine encephalitis (E.E.E.) and in only 5-10% of Western equine encephalitis (W.E.E.). Note that paralysis without sensory changes or signs of cerebral deficit nearly always signifies paralytic polio-myelitis.[6]

Differential Diagnosis

The important non-viral diagnostic possibilities to be considered in a patient with encephalitis may be grouped as follows:

(a) *Bacterial* Bacterial meningitis, T.B., pertussis, septicaemia;

(b) *Other Organisms* Leptospira, syphilis, relapsing fever, epidemic and scrub typhus, Rocky Mountain spotted fever, trypanosomiasis, toxoplasmosis, cerebral malaria, trichinosis, schistosomiasis, cysticercosis;

(c) *Degenerative* MS and other neurological degenerative diseases;

(d) *Immune* SLE, glomerulonephritis;

(e) *Metabolic* Diabetic coma, hypoglycaemia, acute porphyria, hypertensive encephalopathy;

(f) *Accidental* Head trauma, poisonings;

(g) *Intracranial Masses* Brain abscess, neoplastic, subarachnoid and subdural haematoma.

EPIDEMIC VIRAL ENCEPHALITIDES

These diseases are produced by members of a large, ever-growing, group of anthropod-borne or "arbor" viruses. Mammals, birds, and arthropods are reservoirs of infection (which is usually inapparent in animals). E.E.E. and W.E.E. cause epidemics of fatal encephalitis in horses, and the Russian viruses elicit a similar disease, louping ill, in sheep. Each virus is characterized by a geographic distribution which is mainly a reflection of the distribution of the preferred host animal. Knowledge of epidemics in animals may assist in diagnosis: for example, in E.E.E. and W.E.E. the illness among humans often follows a previous outbreak among horses; horses are referred to as the *indicator species*. Insect vectors pick up the virus from the animal reservoir and transmit it to man, the accidental host in their bite; e.g., ticks, mosquitoes. The seasonal incidence of the arbor encephalitis epidemic probably depends on the idiosyncrasies of the life cycle of the particular insect vector involved. The commonest (which means least exotic) of the arbor viruses known to cause epidemic encephalitis are the following six — E.E.E., W.E.E., St. Louis encephalitis, Japanese B encephalitis, Murray Valley encephalitis and Russian S.S.E. The names indicate the location of the epidemics which resulted in the serotypic identification of the particular arbor virus involved. Subsequent outbreaks have occurred in other localities, such as the Florida outbreak of St. Louis virus.[7]

Pathology

In all cases there are widely distributed lesions in the nervous system, including haemorrhages, mononuclear perivascular exudates, neuronal degeneration and necrosis and advanced focal demyelination. In Japanese B and Murray Valley infections there is extensive destruction of the Purkinje cells.[8]

Specific Disease Entities

1. *The Equine Encephalitides*

Subclinical infection occurs commonly (5-10% of cases) in epidemic areas in W.E.E., rarely in E.E.E. E.E.E. is much more severe than W.E.E. with a 50-75% mortality and a high incidence of serious residual defects, such as, paralysis or mental deterioration. C.S.F. pressure is high, protein concentration elevated, and an initial polymorphonuclear pleocytosis of 1000 gives way to predominance of mononuclear cells in a few days.

2. *St. Louis Encephalitis*

St. Louis encephalitis affects both young and old. Inapparent infection is remarkably common. In children convulsions are more frequent, mortality high (30%) and sequelae common (25%). In adults we find lethargy and disorientation, 5% mortality, and rarely serious sequelae.

3. *Japanese B and Murray Valley Encephalitis*

Japanese B and Murray Valley (Australia) encephalitis are produced by closely related, but distinctly different, viruses. The pathology is the same for both. Infection is common but carries a low mortality in view of the overwhelming number of asymptomatic cases. However, among individuals who develop clinical disease, fatalities are all too common (40 to 60%). For those who survive convalescence is long and slow. Lethargy, weakness, tremors and anorexia may persist for weeks. Extensive weight loss is frequent and a large porportion of patients show impairment of mentation, personality change or paralyses which persist.

4. *Russian Spring-Summer Encephalitis*

The Russian tick-borne complex produces a strikingly biphasic disorder. A febrile influenza-like illness remits and is followed in four to ten days, in a proportion of cases, by fever, severe headache, and neurologic manifestations. Defervescence usually follows in 10-12 days and convalescence usually ends in complete recovery.[9]

Diagnosis

Since virus isolation is a retrospective (autopsy) procedure, only serologic tests are relied upon for the diagnosis.

Control

Other than attempts to control vectors in local areas and the use of screening, protective clothing for individuals entering endemic zones of infection, specific immunization is the only approach that offers hope.

ENCEPHALITIS LETHARGICA
(von Economo's Disease)

Encephalitis lethargica was the name given to an epidemic of viral encephalitis in the 1920's studied by von Economo. Burnet says the virus, which flourished in 1923, is now extinct.[10] The importance of the disorder today lies in the fact that we have been left with a number of cases of post-encephalitic Parkinsonism, a complication which fortunately has not gained notoriety in association with other viral encephalitides.

ACUTE DEMYELINATING ENCEPHALITIS

A.D.E. is a term used to group together the post-infectious and post-vaccinal encephalitides. These are sensitivity reactions which may follow upper respiratory infections, measles, chickenpox, and vaccinial or rabies vaccinations within 4-12 days. The encephalitis syndrome produced resembles those already discussed. The disorder is distinguished from acute disseminated sclerosis only be by the fact that remissions and relapses do not occur. Neuromyelitis optica is a variant characterized by massive demyelinization of the spinal cord and both optic nerves following an upper respiratory infection. ACTH is beneficial in acute demyelinating encephalitis, although caution must be exercised in administering this to a case of chickenpox. The care of the paralysed and incontinent person is similar to that discussed later under polio. The mortality rate is high in neuromyelitis optica and in post-vaccinal encephalomyelitis but is low in post-exanthematous cases. If the patient survives, the recovery may be remarkably complete and second attacks are very rare. Of course, the incidence of occurrence, mortality and sequelae of A.D.E. varies widely with the virus responsible; for example, the occurrence and hazards of post-measles encephalitis are much greater than those of varicella.[11]

Recent Findings in the Field of Viral Encephalitis

Epidemics of neurolabyrinthitis (epidemic vertigo)[12] and of cervical myalgia[13] for which viral etiologies are postulated have been described.

Work on the neuroparalytic accidents associated with polio vaccine have shown that the allergic inflammatory response operating in the immune type of encephalitides depends on a elevation of antibody level occurring at a critical time during virus multiplication in the C.N.S.; encephalomyelitis and demyelination occur just when serum antibody is becoming detectable. Cold and increased CO_2 tension are found to increase permeability of the blood-brain barrier and allow antibody to reach the nervous system earlier, increasing the risk of disease.[14]

Herpes infections of the hypothalamus, upsetting the sodium-regulating centres and giving rise to salt retention syndromes have been described.[15]

POLIOMYELITIS SYNDROME

COXSACKIE AND ECHO

While this category admittedly overlaps that of the Viral Encephalitides, clinically it differs sufficiently to warrant its separation for purposes of this discussion.

Coxsackie B is a well recognized cause of encephalomyocarditis in children. Coxsackie virus has been recovered from the CSF of cases that otherwise appeared clinically the same as polio.[19] It is likely that many reported cases of polio, where the virus has not been found, have been due to Coxsackie and ECHO infections. ECHO mimics clinical polio as well, but, superimposed on the poliomyelitis syndrome, there may be manifestations of drowsiness, disorientation, convulsions and optic neuritis.[20] In the Hospital for Sick Children in Toronto in 1957 a large number of cases of ECHO 6 and 9 aseptic meningitis, usually associated with rash, conjunctivitis or small mouth abscesses, were reported. In 1936 ECHO 9 was again dominant in Toronto, but this time without the rash.[21] Multiple attacks of enteric viral infections can occur in the same person, as a single infection does not confer lasting immunity subsequently. Coxsackie and ECHO are recognized by isolation from the faeces. Onset of the disease may be heralded by low fever, swollen lymph

glands of the neck, headache, fatigue and muscle pain. Reticuloendothelial involvement is common. Muscle weakness, mild paralyses, increased tendon reflexes, neck rigidity, photophobia, irritability and occasionally cranial nerve palsies and pyramidal system involvement are found. Recovery is slow and convalescence prolonged.

POLIOMYELITIS

Although now a relatively unimportant disease, polio serves as a useful prototype or model in discussions of viral neurological disorders. For this reason, it is presented in more detail than some of the more common but less well studied N.S. infections.

Definition

Poliomyelitis comes from the Greek "polios" (gray), plus "myelos" (marrow), plus "itis" (infection). The causative virus damages chiefly the anterior horn cells in the grey matter of the spinal cord and brain stem. These subsequently undergo necrosis followed by paralysis and wasting of the muscles they innervate. The infection is self-limiting and may die out before actual paralysis occurs.

Etiology

The causative agent is an RNA-containing spherical virus 28 millimicrons in diameter.[22] Three antigenically distinct types are recognized, 1, 2 and 3. With the advent of tissue culture of polio viruses, the door to modern experimental virology was opened.[23]

Pathology and Distribution of Lesions

The virus enters the mouth in faecally contaminated water, food, and plants and multiplies in the oral pharynx and intestine. Spread to the central nervous system follows a viraemia which persists only a few days until antibodies make their appearance. The virus gains a foothold in the nervous system and reaches neuronal cells by spread along nerve fibers. The areas of the central nervous system affected[24] are:

1. the anterior horn cells,
2. the motor areas of the cortex (pyramidal cells),
3. the subthalamic, cerebellar and vestibular nuclei,
4. the gray matter of the brain stem, mid brain and medulla, and
5. any combination of these.

The virus multiplies intracellularly, its RNA presumably appropriating normal neuronal metabolites for its own replication. The chemical and morphological by-products of the cell damage so induced are responsible for the clinical symptoms.

Histologically, a non-specific inflammatory response is initiated in the gray matter and gliosis soon appears. The perivascular sheaths are distended by cells which are poured out into the subarachnoid space to reach the CSF,[24] accounting for the early polycytosis and subsequent lymphocytosis seen in spinal tap specimens.

Epidemiology

Poliomyelitis is a world-wide disease. The fact tha there is widespread distribution of neutralizing anti body in healthy populations means that polio is muc more prevalent than is suggested by the number o clinically recognized cases. As much as 95% of the di sease is said to be clinically inapparent.[25] Epidemics ten to occur more commonly in the summer and where poor sanitation prevails. Host factors influencing the in cidence and severity are the presence of type-specific neutralizing antibody (less likely to be present in th young, excepting newbornes protected by materna antibody), pregnancy (resistance lowered) and recen trauma to the oral pharynx, especially tonsil and aden oid operations in children. Chilling or physical exertio after invasion by the virus leads to more frequent de velopment of paralysis (relate to section on Recen Findings in the Field of Viral Encephalitis—regardin cold, carbon dioxide increasing the blood-brain bar rier's permeability to antibody).

Clinical Manifestations

Symptomatology is sometimes classified as *pre-para lytic* or *paralytic* and under the latter, *spinal and bulbar* A more comprehensive organization is the following:[2]

A. *Inapparent Infection*

The virus is present in the gut and antibody develop in the blood but there are no symptoms. Ninety pe cent of poliomyelitis is in this form.

B. *Minor Illness*

This is an abortive fever associated with mild upper respiratory infection, gastrointestinal or arthritic symptoms without clinical or laboratory evidence of central nervous system invasion.

C. *Non-Paralytic Poliomyelitis*

A Minor illness — prodrome is followed by signs o meningeal irritation and abnormalities of the spina fluid. A differential diagnosis is difficult and include healing bacterial meningitis, tuberculous meningitis focal embolic encephalomyelitis (from subacute bac terial endocarditis), scarlet fever, post-vaccination per tussis encephalopathy, leptospiral meningitis, Coxsackie virus infections, HS meningitis, infectious mononu cleosis, trichinella meningitis, brain abscess, MS, brain and cord tumours, C.N.S. allergic reactions, post-in fectious encephalitides, infectious polyneuritis, and LCM. Mumps meningitis without salivary gland involve ment and Coxsackie virus disease are the most importan differentials. Defervescence occurs in three to five days with no changes or abnormalities detected in reflex muscle or cranial nerve function. Meningeal irritation takes two weeks to clear.

D. *Paralytic Poliomyelitis*

Following a progression through A, B and C, signs of involvement of motor cells in the spinal cord and brain or cranial nerve nuclei are observed, resulting in

paresis or paralysis of various muscle groups. Paralytic polio has been further subdivided into the following types, depending on the distribution of paralyses:

A. Sensory

Notice that sensory losses do not accompany poliomyelitis. The only sensory manifestations are *cramping pain* in the affected muscles and *hyperaesthesia* of the overlying skin, both of which *precede the paralysis.*

B. Motor

i) *Lumbar — Paralysis* may follow the pain slowly or suddenly. Hemiplegia, quadriplegia and monoplegia may result, as well as *urinary bladder dysfunction.*

ii) *Thoracic* — Paralysis of the *respiratory muscles* follows thoracic spinal cord involvement. Constipation, abdominal cramps and tympanites occur with *partial ileus.*

iii) *Cervical* — Cervical lesions may paralyse the diaphragm by involvement of the *phrenic nerve.*

iv) *Brain Stem* — Bulbar involvement is commonest in children subjected to T & A operations. Involvement of *cranial nerve motor nuclei* can give rise of ocular palsies, pupillary disorders, masticatory and facial paralyses, vestibular dysfunction, voice changes, dysphagia, laryngeal stridor and aspiration. *Respiratory centre* involvement causes serious interference with the rate, rhythm and depth of breathing. *Cardioregulatory centre* involvement can cause upsets, varying from hypertension to irreversible shock.[27]

v) *Cerebellum and Cortex* — Polioencephalitis may cause *focal* cortical manifestations or, in its more *diffuse* form, cause confusion, agitation, uncontrolled spontaneous movements, insomnia, lethargy and eventually death. The diagnosis of paralytic poliomyelitis can usually be made on clinical grounds. Confirmation is by isolating the virus, (throat swabs, faeces) and demonstration of a rising serum antibody against one of the three serotypes using paired serum samples. Two polio antibodies are known, one peaking very quickly in disease, the other appearing as early but lasting for years.[28]

C.S.F.

Pre-paralytic changes include elevation (30-300 per cubic millimeter) of polymorphs followed within days by lymphocytes. In the first week protein levels rise from 30 to 60 mgm%. In the second and subsequent weeks the cell count may fall, reaching normal by the third week, while protein continues to 100, 200, even 300 mgm%.[29]

Complications

Myocarditis may be caused by polio virus. Fluid and electrolyte disturbances may occur secondary to respiratory dysfunction. Furthermore, hemodynamic disturbances secondary to the artificial respiration needed also occur. Pulmonary infection can complicate a tracheostomy performed to aid respiration. Urinary tract infections accompany bladder catheterization.

The pareses and paralyses are asymmetric and inconstant. After the second month the affected muscles may be classified into the following categories:

1. totally denervated,
2. partially denervated (slight recovery possible),
3. minimally involved (no decrease in function).

This categorization serves as a basis for prognosis. Following the wasting of muscles there are contractures which, if untreated, cause deformity (e.g., kyphoscoliosis from involvement of the back muscles). There may also be damage to unprotected joints. Psychiatric complications can occur in severely crippled persons, especially those whose lives are threatened by respiratory difficulty. They frequently suffer anxiety and depression, and acute psychoses have been reported.[28]

Treatment

Treatment is aimed at 1) relieving the symptoms, 2) averting the complications and 3) rehabilitating the patient. As you may expect, this can include bed rest, analgesics, treatment of fever, local application of warmth, passive exercise and, later, active exercise in the swimming pool. Where the complications call for it, one can employ tracheostomy, electrophrenic or tank respirators, tube feeding, antibiotics for respiratory and urinary infections, social service help, corrective surgery and orthopaedic devices to support the weakened back and limbs.[30]

Prognosis

Overall mortality is 5%, being worse with bulbospinal involvement (cardiorespiratory centre) and influenced by age, development of complications, and sites and extent of C.N.S. infection.[28] Every case carries an individual prognosis according to the distribution of lesions. Predictions regarding prognosis cannot be made on the basis of the severity of pre-paralytic symptoms and may not be possible until months after onset. There is no significant motor recovery beyond seven months.

Prevention and Polio Vaccines

Isolation is next to useless since we are exposed to so many carriers and subclinical incubators of the virus. *Gamma globulin*[31] has now been superceded by active immunization procedures. *Salk vaccine* was heralded as the panacea for polio when it was introduced in the United States. Subsequent immunizations were indeed achieved but there were notable failures in up to 30% of cases in certain areas of that country. These are now thought to be due to the low antigenic potency of certain lots of the vaccine and failure to give a fourth

dosage (booster). The presently available vaccines are said to be much improved in potency and standardization.[32] Oral vaccines are now on the market and seem to offer several advantages over the killed or Salk type. The viruses used are low virulence, high antigenicity, thermostable strains that infect the G.I. tract of the recipient (without harm) and thereby exclude pathogenic polio from implantation. The attenuated virus spreads and infects contacts. An antibody response is achieved which is better and longer lasting than that obtained with killed virus vaccines. Over 90% protection against paralytic poliomyelitis is thereby achieved and there is a tendency for the epidemic polio strains to be replaced by those of the vaccine. The possibility of back-mutation of the vaccine virus to a pathogen has been considered. Such mutation does occur, but only to a plateau of increased pathogenicity which is below that thought to be dangerous for man. *Interference* is a phenomenon which occurs if vaccination with the live type of polio vaccine is attempted during a period when other enteroviruses are inhabiting the patient's G.I. tract. Their presence interferes with implantation of the vaccine strain and thereby blocks the immunization. In Canada the Sabin trivalent live vaccine is licensed for use in adults and improved Salk vaccine is given to children. A booster dose is necessary in the case of live vaccines carrying more than one strain as the combination of three strains produces some interference.

ASEPTIC MENINGITIS

Definition

Aseptic meningitis is a symptom complex consisting of fever, symptoms of meningeal irritation (headache, stiff neck, Kernig's sign) and an abnormal C.S.F. The C.S.F. findings consist of pleocytosis (mainly lymphocytes) and bacteriologic sterility.

Etiology

Goldfield[15] has proposed the following classifications of the etiology of lymphocytic pleocytosis (modified):

I *Non-infectious Factors*

(a) *Mechanical Irritations of the Meninges* Abscess, operative trauma, spinal anaesthesia, myelography.

(b) *Toxic Factors* Heavy metals, toxins, drugs.

(c) *Neoplastic Lesion*

(d) *Allergic Factors* Post-rabies vaccination, serum sickness.

II *Infectious Factors*

(a) *Bacterial meningitis* M. tuberculosis, L. monocytogenes.

(b) *Mould and Yeast Infections* Cryptococcus, monilia, coccidioidomyces, blastomyces.

(c) *Spirochetal Infections* Treponema pallidum, Leptospira.

(d) *Rickettsial Infections*

(e) *Protozoal Infections* Plasmodium falciparum.

(f) *Helminthic Infections* Trichinella spiralis.

(g) *Viral Infections*

(h) *Presumably Viral Infections,* such as the post infectious encephalitides and acute haemorrhagic leukoencephalitis.

III Disease of Unknown Etiology

(a) *M.S.*

(b) *Periarteritis nodosa.*

(c) *Sarcoidosis.*

Of all the above causes viral and presumably viral II (g) and II (h), are by far the commonest. A breakdown of aseptic meningitis in the U.S.A. in 1955-56 reveals the following incidence of etiologic agents:

Coxsackie 15%
ECHO 16%
Polio 15%
Leptospira 3%
Herpes 1%
L.C.M. 9%
Mumps 12%
All Others
(Some Viral) 29%

Differential Diagnosis

The C.S.F. findings in aseptic meningitis may be organized as in Table 1.

Unless we attempt to arrive at an etiological diagnosis we will fail to pick up the non-viral aseptic meningitides that are amenable to specific therapy. The concentration of glucose is almost always normal in viral infections. Pleocytosis in spinal fluid that shows low glucose and bacteriologic sterility should suggest tuberculous meningitis, cryptococcal meningitis or rarely sarcoid, lymphoma or metastatic carcinoma. The diagnosis of post-infectious or post-vaccinal meningoencephalitis is usually made on the basis of recent illness or innoculation. Infections by enteroviruses and arbor viruses are likely to be encountered in epidemics along with cases of frank encephalitis, and the arbor viruses tend to occur in certain geographic areas, facilitating early clinical recognition, although specific identification of the virus involved may be quite difficult. Lepto-

Table 1: C.S.F. findings in aseptic meningitis.

AGENT	CELL COUNT: AVERAGE	CELL COUNT: RANGE	PREDOMINANT CELL TYPE	GLUCOSE	PROTEIN (Mg%)
Viruses	50-500	15-2000	Lymphocyte	Normal	10-100
Yeasts	50-100	15-10,000	Lymphocyte or Poly	Reduced	100-500
Spirochaetes	50-100	25-200	Lymphocyte	Reduced	10-100
Bacteria	1000-5000	10-100,000	Polymorph	Normal	100-2000

spirosis peaks in August, mumps and IM in March and April. Leptospirosis is the most important non-viral cause of aseptic meningitis and accounts for more than ten per cent of cases in some areas.[18]

Lymphocytic choriomeningitis, acquired by direct exposure to mice or inhalation of infected mouse excreta in dust, manifests itself as a influenza-like respiratory illness with neurological signs appearing only as late complications. Serologic studies indicate that inapparent or unrecognized infection is common in the population. The virus is present in the blood, nasopharynx and urine during the respiratory illness and in the spinal fluid during meningitis. LCM is common in late fall and winter, the period when field mice enter dwellings.[18]

Bennett and Adams drew attention to a clinical situation that is all too frequently seen. "Patients with pyogenic meningitis who are given antibiotics in inadequate dosage without examination of the spinal fluid may be seen at a time when infection has been suppressed to the point that lymphocytes predominate, glucose is normal, and organisms are not detectable in the spinal fluid, a mistaken diagnosis of aseptic meningitis is made and the true state of affairs becomes evident only when the patient worsens and bacteria again appear." [18]

History often gives other clues. A definite history of mumps aids in excluding this disease, second attacks being unusual. A history of syphilis should be carefully ferreted out. Exposure to animals such as mice (LCM), dogs, rats, swine (leptospirosis), or mosquitoes (arboviruses) may give a hint as to etiology. (Occupational exposure to leptospirosis by veterinarians is worth noting.) Clinical signs will give further indications of etiology. Sore throat, lymphadenopathy, or rash point to IM or ECHO infection. Severe back and leg pain occur in poliomyelitis, leptospirosis, and trichinosis. Aseptic meningitis associated with pregnancy is likely to be poliomyelitis. The presence of any condition known to predispose to brain abscess, such as otitis media, sinusitis, bacterial endocarditis, and pneumonia, constitutes important information. Salivary glands and testes should be examined; minimal involvement may the only indication of mumps. Icterus suggests IM or leptospirosis. X-ray may show pulmonary infiltrates, a clue to diagnosis of LCM, leptospirosis, IM or psittacosis. Laboratory findings are almost all non-specific (leukopenia, leukocytosis, etc.) Eosinophilia may suggest a parasitic infection, and IM and lupus may be recognized by blood smears. Wasserman tests must be interpreted with caution because many disorders, other than syphillis, can produce positive reactions (e.g., IM, lupus).

In summary, constant attention must be paid to the possible presence of tuberculosis, cryptococcosis, syphilis, brain abscess or inadequately treated pyogenic meningitis masquerading temporarily as the syndrome of aseptic meningitis. In any patient suspected of viral meningitis acute and convalescent sera are properly collected. Specimens of faeces, nasopharyngeal secretions, blood, cerebrospinal fluid shall be transmitted to the laboratory.

MYXOVIRUSES: RABIES*

It is appropriate to discuss more fully the Myxoviruses (which belong in the Viral Encephalitis group), since these are of particular importance in this geographical region.

Definition

Rabies is a fatal infection of the nervous system transmitted in the saliva of rabid animals. There are two types of rabies virus, called *street* and *fixed* virus respectively. The former designates the agent of naturally occurring disease, while fixed viruses are rapidly multiplying strains used in vaccine production which have lost their infectivity through repeated passage in laboratory animals.

Epidemiology and Pathology

Stray dogs, bats, foxes, squirrels and wolves may transmit rabies virus to man. The disease in animals is characterized by progressive irritability, frothing at the mouth and vicious, indiscriminate attacks on all creatures and inanimate objects with eventual exhaustion, paralysis and death.[20] Bats are capable of harbouring the infection without manifesting the disease, and hence maintain an ever-shifting reservoir of infection. After the bite of a rabid animal the virus enters the traumatized axons of the victim and ascends the sensory nerves to the CNS. Focal, haemorrhagic inflammation and demyelination, most marked in the basal ganglia, subcortical areas and spinal cord, result. The presence of eosinophilic intracytoplasmic inclusion bodies (described by Negri in 1903) is pathognomonic of rabies. They are found in greatest abundance in the hippocampus and to a lesser extent in the pyramidal cells of the cerebral cortex, Purkinje cells of the cerebellum and nuclei of the basal ganglia. These bodies are not infective and do not seem to be virus aggregates but rather degenerate protein deposits arising from the neuron-virus interaction.[33]

Manifestations and Laboratory Findings[28]

Symptoms come on following an incubation period of 30 to 70 days, (shorter in the case of facial or multiple bites). The patient may first notice a tingling paraesthesia or pain at the site of the bite which radiates to distal parts of the involved extremity. This is followed by a phase of excitement, resembling that described for the animals. Most characteristic are severe, painful contractions of the pharyngeal muscles, initially precipitated by attempts to swallow water. Consequently, patients

The committee on nomenclature has not yet approved the inclusion of Rabies in the Myxovirus group; it has only been suggested.

manifest a fear of water (hydrophobia) and to avoid swallowing, allow frothy salivy to drool from the mouth.

Laboratory findings include a systemic leukocytosis (polymorphonucleocytes and mononucleocytes). Glycosuria, acetonuria, proteinuria, and oliguria are present in most cases. *CSF is normal.* Serum antibodies are present. At autopsy Negri bodies can be demonstrated and rabies virus is frequently isolated from the brain. Rabies is invariably fatal. However, every patient should receive all possible supportive treatment in the hope that the diagnosis is in error.

Differential Diagnosis

1. *Hysterical reactions to dog bites.*
2. *Allergic encephalomyelitis* caused by rabies virus.
3. *Poliomyelitis.*
4. *Guillan-Barre syndrome,* (a presumed viral encephalitis characterized by absence of fever, muscular pain, motor weakness, arreflexia and increase in C.S.F. protein without increase in cells).
5. *Tetanus* (which is distinguished by the development of trigenimal motor involvement and lockjaw).

Treatment and Control

Although the *disease* is invariably fatal, *exposure* to rabies virus is not. Approximately 50,000 persons each year are considered to be exposed to rabies and receive vaccine treatment. Semple vaccine prepared from fixed virus grown in rabbit brain and inactivated with phenol has had the widest use in the United States. Fourteen daily innoculations into the abdomen are recommended. These innoculations will provoke an antibody response (active immunization) before the end of the lengthy incubation period, hopefully in time to avert clinical disease. To afford initial protection in the time when so-induced antibodies are building up but have not yet reached effective levels, passive immunization with anti-rabies horse serum is added. Local treatment of bites consists of scrubbing with detergent and infiltrating with immune serum. The Semple vaccine carries two hazards: 1) local sensitivity reaction in 5% of innoculations; and 2) allergic encephalomyelitis caused by rabid brain tissue in about one out of five thousand vaccinated individuals. Two live vaccines are in use, the Flury strain (prepared in chick embryos and, thus, free of brain tissue) and a duck embryo vaccine. The Flury vaccine is used mainly in animals, the latter in human innoculations.

Vaccine should be administered promptly if a person is bitten by an animal that escapes, that is clinically rabid or shows histological evidence of infection. Healthy animals that inflict saliva-contaminated scratches should be impounded seven days for observation. Immune serum should be administered to all individuals who incur severe or multiple bites.[34] No specific treatment is available once clinical manifestations develop. Barbiturates, fluids, and isolation are the victims' only support to the end.

Other Myxoviruses

Influenza and *mumps* encephalitis are the most important and common enchephalitides seen in Toronto, and measles encephalitis has great importance in paediatrics. Since the pathology and clinical manifestations are very similar to those of the other "Viral Encephalitis" disorders, the reader is referred to this earlier section.

HERPES VIRUSES

Finally, more detailed discussion of the Herpes Viruses, with reference to the V-Z (varicella-zoster) virus* in particular, is indicated. The V-Z virus presents a clinical entity distinct from any of those previously referred to.

Definition

This is an acute, vesicular eruption of the skin within a dermatome, caused by inflammation of the dorsal nerve roots or the sensory granglia of cranial nerves V and VII.

Etiology

The V-Z virus is the causative agent of two diseases —chickenpox and herpes zoster. The former arises in completely susceptible, and the latter in the partially immune, subject.[35] In zoster the virus is demonstrable only in the skin lesions.[36] The inflammatory reaction (which is a constant finding in the segmental nerve, its sensory ganglion, and the posterior horn of the cord) is probably of the immune type. Both the skin and CNS lesions have characteristic pathologies.

Manifestations

Onset is heralded by a brief fever and malaise with pain at the site of the future eruption. On the fourth day (just after you have pronounced a diagnosis of biliary colic, pleurisy or duodenal ulcer) an erythematous dermatitis appears which quickly becomes papular and vasiculated. The associated pain is intense and not completely controlled by analgesic drugs. Zoster lesions are almost always unilateral. Although the trunk is the most commonly involved area, infections of the first (ophthalmic) branch of V occurs and the cornea, sclera or ciliary body are likely to suffer permanent damage.

A serious complication is the development of post-herpetic neuralgia which is common in the aged. Agonizing pain may persist for several months.

Fluid from the unruptured vesicles is bacteriologically sterile. Cerebrospinal fluid changes are unremarkable.

Differential Diagnosis

The differential diagnosis is from pleurisy, appendicitis, pleurodynia, collapsed intervertebral disc, and

**Herpes simplex is a much more common cause of encephalitis and aseptic meningitis; see under Viral Encephalitis, Etiology (other than arbor).*

lumbago, and is very difficult in the pre-eruptive stage. When the unilateral dermatome eruption appears, diagnosis is simple. Sequelae are rare except in the case of zoster ophthalmia where impaired vision frequently results.

Treatment

Treatment is aimed at minimizing the patient's discomfort and preventing secondary bacterial infection. Complete bed rest, aspirin, codeine, and mild sedation are essential during the acute phase. Collodion dressings have little analgesic effect but reduce the frictional irritation of clothes and decrease the risk of infection. Where indicated, antibiotics are used to control secondary infection. In ophthalmic herpes, an ophthalmologist is called in. Both oral and local antibiotics, guided by culture and sensitivity tests, and cortisone to control inflammation are employed. The multiplicity of recommended procedures for dealing with post-herpetic neuralgia only serves to reflect the shortcomings of each. Among those that have been advocated are injection of the dorsal root with alcohol, dorsal rhizotomy, cordotomy, procainization or excision of skin, paravertebral block, autohemotherapy and sympathetic ganglionectomy.[43]

CONCLUSIONS

In this paper some of the unknown facts of viral infections of the nervous system have been organized in a manner that follows logically from the classification of viruses presented to second year medical students at the University of Toronto. Further, there has been an attempt to correlate the clinical findings and therapy with the presumed *modus operandi* of the viruses concerned.

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Bacteria and their Viruses

The ready availability of bacteria and their viruses (bacteriophages) make them excellent material for studies on virus structure and life cycle. These photomicrographs illustrate 2 stages in the life cycle of a bacterial virus.

Answers on page 123

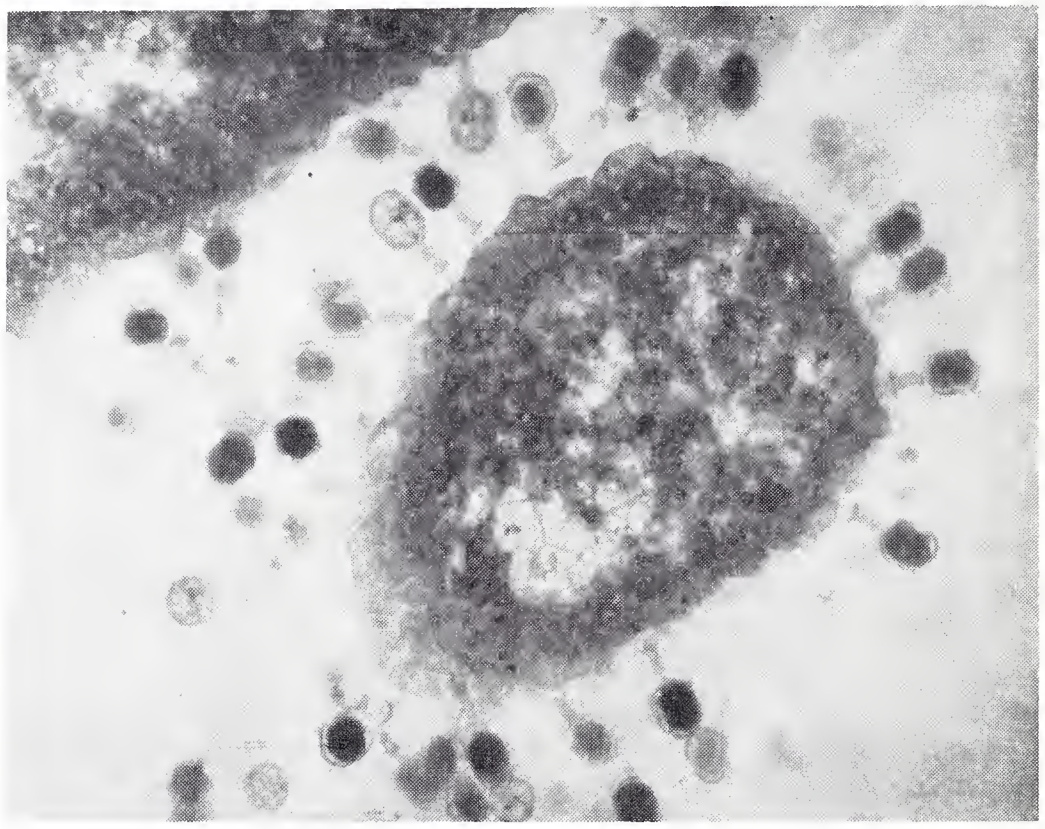

Figure 1:

1. How do the structures of the bacteriophage and cell virus differ?
2. Of which stages in the bacteriophage life cycle are Figures 1 & 2 representative?
3. Compare the stage shown in Figure 1 with the similar stage in the cell-virus life cycle.

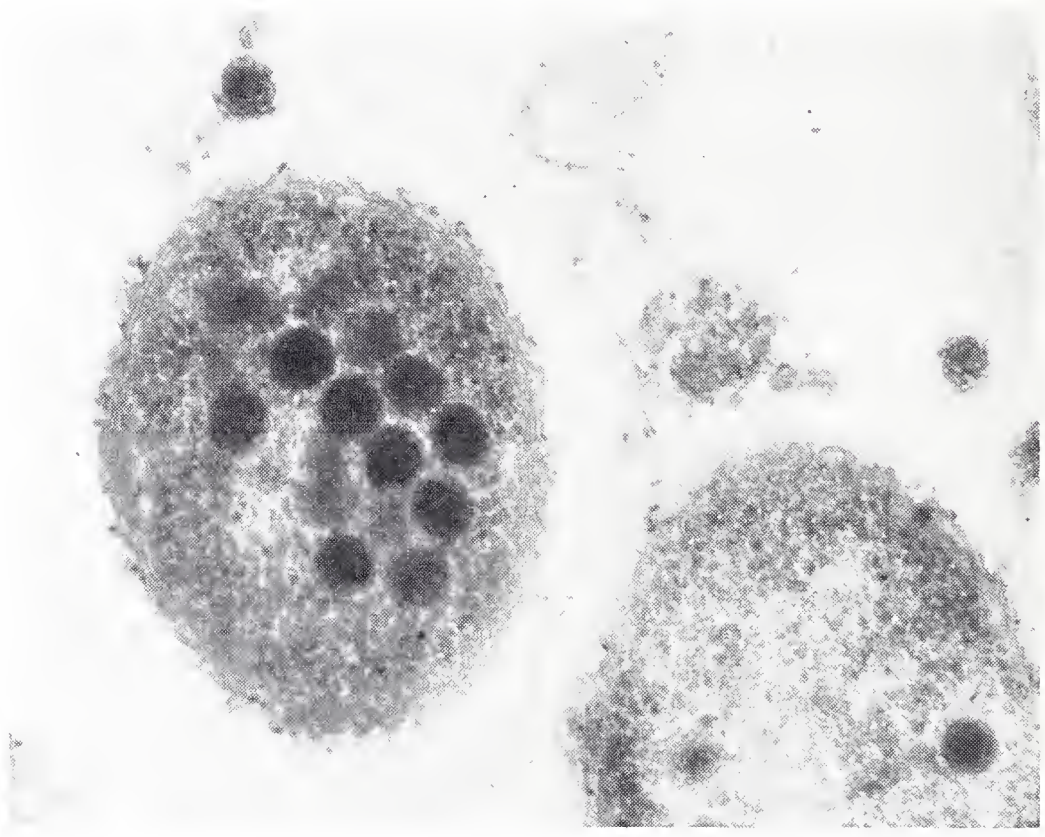

Figure 2:

1. Viral infection does not always result in cellular death. What genetic alterations can take place? How do such alterations offer a possible explanation for malignancy?

The Virus of Infectious Hepatitis

M. N. Kroch B.Sc. (Med.) 6T5

The past twenty years have been replete with examples of the isolation and characterization of many viral agents pathogenic to mankind. Although routine diagnostic laboratory facilities employing modern techniques in animal and tissue culture are now available to physicians throughout this country, it is somewhat surprising to note that at least one relatively common viral disease has not benefitted from the remarkable advances in viral research. This viral syndrome, which appears to be lost in the realm of modern medicine, is commonly known today as infectious hepatitis. It is by no means merely "a disease of the times" for as far back as 377 B.C. Hippocrates reported an epidemic of fever and "yellowness". Through the centuries the condition has been variously known as icterus epidemica, catarrhal jaundice and epidemic hepatitis.

A. VIROLOGY

To comprehend the clinical-pathological picture of hepatitis, it was essential to differentiate the etiological agents. To this end, the virus of yellow fever was one of the first to be isolated in laboratory animals, maintained in tissue culture, attenuated as a vaccine and effectively attacked as an epidemiologic problem. This left the viruses of infectious and serum hepatitis to the scrutiny of the medical profession. After Cockayne[2] noted the relationship between acute yellow atrophy and infectious hepatitis, Eppinger described the pathology of the condition as "acute yellow atrophy in miniature". Just before the second world war when injectable medicaments were first widespread, serum hepatitis was differentiated from its counterpart, infectious hepatitis.

By 1942, it was shown that infectious hepatitis could be induced in human volunteers by feeding duodenal fluid, urine or blood from patients with hepatitis. The task was obvious — isolate the virus; however, most investigators met only failure in their attempts to introduce the virus into animals, embryonated eggs or tissue culture. Henle et al[5] had some success with a chick-embryo technique but this egg-cultivated virus failed to demonstrate consistent clinical and pathological changes in culture or produce consistent clinical hepatitis in human subjects. In 1956 and again in 1959, Franklin et al[4] were unsuccessful in growing the virus in human tissues, in monkey tissues or in Detroit-6-cell tissue culture.

Rightsel[8] was the first to publish work describing a positive isolation of the virus and meet the critical judgement of a doubting profession hardened by years of experience in assessing similar claims. Doubt was cast for two reasons. First, confirmation by other workers was deficient and secondly, the tissue culture required human serum and great experience in recognizing the cytopathologic effect. More results were forthcoming from Rightsel's laboratory in 1961[9] wherein he described viral isolates obtained from the inoculation of human plasma or serum into Detroit-6-cells, a cloned strain of epithelium-like cells derived originally from the bone marrow of a patient with bronchogenic carcinoma. There have since been other confirmatory reports.[1,11]

McLean[6] recently described these viral isolates as a culturally and morphologically similar group to which his term of reference was "hemoviruses". In discussing the properties of these viruses, this investigator suggests that there are at least three serotypes, similar in size and other characteristics, which are very limited in the number of mammalian cell cultures in which they may produce a characteristic cytopathological effect. The virus is capable of passing a filter with pore diameters of 20 mμ. On electron microscopy, the virus has been visualized as spherical or icosahedral particles of approximately 15 mμ diameter. A sedimentation constant of 18 to 20 S and a density of 1.28 in aqueous media has also been attributed to the virus. It is further characterized by an ability to resist inactivation by ether and other chemicals and can withstand a temperature of 60 degrees centigrade for more than four hours.

B. PATHOLOGY

The present concept of the pathological picture associated with epidemic hepatitis has been limited because knowledge of the benign form of the disease has been gleaned predominantly from liver biopsies. According to T.B. Mallory, the significant microscopic features of this condition are six in number:

(1) Periportal inflammatory infiltration, largely by histiocytes and lymphocytes:

(2) Foci of intralobular infiltration by similar cells;

(3) Lobular disarray (distortion of normal liver lobule architecture as a result of irregular swelling of liver cells);

(4) Hyaline necrosis affecting single cells;

(5) Evidence of regeneration (mitotic figures in liver cells);

(6) Bile stasis.

Wilner et al[12], using time-lapse interference contrast microcinematography, have demonstrated the progressive development of the cytopathological effect and differentiated it from that produced by other viruses.

More recently, Dunnebacke[3] described electron microscopic observations of liver cells inoculated with "lipovirus", a transmissible cytopathic agent arising from serum of a patient with infectious hepatitis. His findings are categorized into three stages: early (after two days), intermediate (after five days), and late (after nine days) manifestations of the infestation. The early picture portrays 25% of cells displaying areas of clumped nucleoplasm randomly mixed with more devoid areas. Nucleoli were frequently vacuolated and the cytoplasm in all cells looked normal. In the intermediate period, the cytoplasm was characteristically vacuolated and associated with swollen mitochondria. Chromatin was usually found centrifugally placed near the margin of the nuclear membrane. The nucleus, though it maintained its round shape, was devoid of its usual fine granular nucleoplasm and nucleolus and contained large masses of particles of two types. Near the nuclear membrane were densely packed particles 10μ in diameter with a smooth outline, while more centripetally placed in the centre of the nucleus were particulate substance of 20-30 mμ diameter arranged in an irregular pattern with spaces between particles. By the late stages, however, evidence of chromatin and particles were absent from the nucleus which by now was one third its normal size. In fact, the whole cell was about a fraction of its normal diameter and contained in its cytoplasm an increased density of mitochondrial reticulum and an increased number of large osmophilic droplets. Characteristic of this stage, almost all sections of the cell contained ring-shaped spongiform bodies, maximal in the cytoplasm and grouped in numbers of two to six. These bodies were also found outside the cell and in cell-free material, possibly implicating themselves as the etiological basis in the great infectibility of this condition.

C. CLINICAL STUDIES

McLean[6] has recently described a new study on prison inmates at the Illinois State Penitentiary in Joliet who volunteered to be exposed to his "hemovirus". In screening these men, 42% were found to have a previous history of jaundice, abnormal liver function tests or definite viremia. Another 12% showed a cytopathological effect suggestive of a virus, but no etiologic agent could be isolated. Using the remaining 46% of subjects, isolates of each of the three serotypes from natural cases were given either intramuscularly or *per os*. He noted that two types definitely caused human hepatitis (fulfilling Koch's postulates), and added that further studies with the third was necessary before a final conclusion could be established about its status. Of the 62 men inoculated, 21 showed clinical hepatitis, 48 showed an increased antibody titre and 61 showed a take.

Viremia was found to occur as early as seven days but usually between 21 to 56 days, at a time corresponding to the onset of symptoms in those who had the disease. It was also discovered that both antibody and virus could be isolated from the same blood sample suggesting that the antibody had a low avidity for virus and seemed to act more by blocking infection of susceptible cells than by neutralizing or destroying the virus.

In this study, transaminase tests were found to be most sensitive and revealed the first functional abnormality seen in liver function tests. This result suggested the possibility of liver function tests in the detection of carriers of viral hepatitis but Stokes et al[10] reported that only two out of three persons proven to be carriers by their ability to infect volunteers had abnormal liver function tests. Direct and circumstantial evidence indicates that the carrier state can persist for at least five years, and of the proven carriers with abnormal tests this abnormality persisted for a similar number of years. Norris[7] thus concludes that although liver function tests are not specific for viral hepatitis, their use, coupled with programs to increase immunity and decrease the risk of exposure, will give gratifying results in reducing infectious hepatitis as a epidemiologic problem in the future.

At the present time there is no definite evidence that any known agents directly attack the virus of hepatitis once it has invaded the liver. This serious limitation forces the physician to direct his efforts toward preventing the disease, keeping the patient alive, arresting the damage and encouraging the regeneration of normal liver cells in every way possible. Since the disease tends to be self-limited and mild in children and young adults, evaluation of therapeutic measures is extremely difficult.

SUMMARY

The work of Rightsel and of McLean in the isolation of the virus of infectious hepatitis is discussed, followed by a description of the pathology found in liver biopsies and in tissue culture. McLean has induced the disease in human subjects, and his findings are listed. Liver function tests may be of aid in disease control. Treatment of established disease is purely symptomatic.

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A Survey of Computers in Medicine

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INTRODUCTION

Computers are instruments with finite infallible memories which, upon receiving data presented by man, process this data quickly according to instructions set down by man.

The key to their usefulness lies in the two words (1) quickly and (2) infallible:

(1) Computers can operate in nano-seconds or billionths of a second. This enables a great number of operations from the same or different "jobs" to be carried out quickly.

(2) Computers now have "memories" which can store 10^9 "bits" of information. Yet the real advantage is not the size of the memory but the fact that it does not fail.

In simplified form, the computer can be explained as follows. Information is fed into the main memory unit via the Input/Output (I/O) unit which converts the data to machine language. The data is then diverted to the arithmetic and/or logic units and operated upon there as directed by the control unit. The results are then directed back to the memory and out of the I/O unit. The power supply holds the voltages and currents constant for proper operations, while the console houses the controls operated by man.

APPLICATIONS IN MEDICINE

Computer applications in Medicine can be divided into five main fields:

1. Business
2. Medical records
3. Research
4. Teaching
5. Diagnosis

1. Business

It will only be mentioned here that hospitals can and do buy time on computers to do some of their accounting, pay rolls and inventory; i.e., the most common application of the digital computer today.

2. Medical Records

A representative example covering most of the aspects of this application is outlined as follows:

The General Hospital in Jacksonville, Florida[1] has developed a standard form to be used by doctors and medical students. Internationally standardized terms are used. The information recorded is as follows: name of patient, name of attending doctor, name of attending medical student, history, physical, diagnosis, treatment and course. This information is then translated into machine language, fed into a computer, stored, and processed. The following results have been obtained:

(1) Records are quickly and easily retrievable;

(2) Treatments are evaluated, discarded, or changed and improved more efficiently;

(3) Drug effectiveness is better determined;

(4) A wide cross-section of cases is assured for the medical students to study.

3. Research

At present, this area of endeavour applies to the computer more than any other area in Medicine. The applications are many and varied. One such application is outlined.

A transfer function is a mathematical property characteristic of a system, just as a spectrograph is a physical property characteristic of an element or substance.

At the Institute of Bio-Medical Electronics of the University of Toronto, a project is under way to determine the transfer function of the heart. A digital computer is used to do the complex and tedious calculations necessary to derive this transfer function. It is hoped that once normal and abnormal transfer functions are determined, the differences in the abnormal transfer function can be related to the abnormalities within the heart. This will enable earlier, more specific and less traumatic diagnosis of cardiac problems.

There are many other applications, a few of which are listed below:

(1) A Cardiac Output Computer for the Rapid Analysis of Indicator-Dilution Curves[2];

(2) Correction to "Analog Computer Studies of Periodic Breathing"[3];

(3) Computer and Data Processing for Nervous System Research[4];

(4) Analog Computer Simulation of a Neural Element[5];

(5) Electrical Analog Simulation of Temperature Regulation in Man[6].

4. Teaching

Teaching computer programs, although not widely used yet, can enable a medical student to augment his bedside experience and skill in diagnostic practice.

An example of such a program was developed by Feurzeig et al[7]. Their description of the program follows.

"The computer program, called the "Socratic System," states a problem to a student, engages him in "conversation," while he attempts to solve the problem. Instruction takes place at the computer console. The "conversation" is accomplished through the use of an electric typewriter connected to and controlled by the computer. The student types a question or an assertion and the computer types back a response—an answer, a comment, or possibly another question.

Before the study session begins, the student is given a list specifying the vocabulary for the problem. During the session, the student's questions and declarations must be chosen from the terms on this list. The vocabulary can be extensive. The student is allowed considerable freedom in his approach to solving the problem. He can specify the information he wants when he wants it, and he can make assertions as to the solution whenever he wishes. The system records the information given to the student. It answers each question or declaration by typing one or more responses from a pre-specified set of responses. The particular responses at any time are determined by the student's knowledge at that point. Each computer response depends not only on what has just been said but on everything that went before.

A few excerpts from the program are given below.

S = Student
C = Computer

S. Physical exam?
C. Fine. What in particular would you like to know?
S. Chest exam?
C. It is common practice in the medical profession to begin an examination by checking the patient's general appearance.
:
:
S. Proceed.
C. Finished? No, doctor! you're stopping short of a reasonably thorough examination.
:
:
S. The Grippe.
C. "La Grippe"? Nonsense!
S. Influenza.
C. Come, come. You know that in influenza there is an absence of almost all positive physical signs, don't you? Review the evidence carefully, doctor.
S. Pleural effusion.
C. A good contender, but let's be careful. What evidence would rule it in or out?
:
:
S. Sputum smear?
C. Gram positive rods.
:
:
S. Sputum culture?
C. Presence of pneumococci.
:
:
S. Pneumococcal pneumonia.
C. Very good. It's obvious now, though there were some confusing signs and symptoms in the picture. You've seen your way through to the correct diagnosis.

Thus, the system responds to the student's question and declarations in the manner of a personal tutor — answering good questions, reproving foolish conclusions, acknowledging perceptive decisions, questioning the grounds of inference, etc. The pedagogic strategies are open; they are a part of the information specified by the teacher who prepares the problem. Directed by these strategies, the system carries on a tutorial dialogue with the student, one in which interesting contingencies may be developed to any arbitrary depth. The system's responses are in free, rich language. The problem under study need not be of stationary character. It can embody a situation which changes with time as the interaction develops. With this versatility, computers can aid students."

5. Diagnosis

Diagnosis has been made possible by training physicians. This training consists largely of storing information in the physicians' memories and programming them to make logical decisions compatible with that information. Perhaps electronic data processing machines have something to offer, for, in its simplest expression, an electronic data processing machine is a device with a large memory which has been programmed to make logical decisions compatible with the information stored in its memory.

Now, a concept of information theory is important to this discussion, that of signal and noise. Signal is desired (or, in effect, correct) information. Noise occurs in medical history taking in the form of misleading and irrelevant replies of the patient, replies based on erroneous recollections or misunderstanding on the part of the physician. A great deal of the art of medicine lies in sorting the signal from the noise. We think of this as an activity requiring intelligence, which a computer cannot have, but actually it is more usually the result of training and experience. A great deal can be done by a computer to improve the ratio of signal to noise, perhaps more than by the human mind, for the doctor's own mind is a noise source as well. We are all familiar with the ease with which we can mislead a patient to give us historical information we are convinced should be there, but which really is not.

Further, during conscious rational thought, few indeed can keep in the forefront of the mind more than a very few facets of a logical problem. This leaves the usual human logical process to be a progressive paramecium-like exploration, a trial and error moving from concept to concept rather than the brute force forward march on all fronts method of which an electronic computer is capable.

Perhaps it is less obvious how a computer may grapple with the sort of information accumulated in medical history taking and in physical examination. This is not an appropriate place for an extended discussion of symbolic logic or Boolean algebra, but it can be noted that computers can be programmed to follow deductive logic processes, for deductive logic proceeds by formally worded statements being manipulated by sharply defined rules, adding nothing but conclusions deduced from the existing information. Deductive logic disciplines our use of what is already known and so fails to fire the imagination with anticipated conquest of new terrain. Fortunately, most of it proceeds in our unconscious. We are thus saved from the brick-by-brick masonry work which erects our conclusions for us seemingly without our participation.

For the work proposed with computers, not the least dismal aspect is the need to spell out to our stupid but logical machine these picayune but essential details of the diagnostic exercise. However, once done, and the background information is programmed, the computer then can:

(1) Produce a list of possible diagnoses consistent with medical knowledge from information, including history, physical and laboratory results, presented by the patient;

(2) Indicate what tests would best differentiate between the remaining diagnostic possibilities;

(3) Calculate the probabilities for the alternate diagnostic possibilities;

(4) Enable a more precise statement and analysis of the value decisions which may be associated with treatment planning. (Such applications must be based on extensive medical data);

(5) Compile statistics that relate symptom-disease combination and evaluate disease-treatment-prognosis results (these statistics are then used in future diagnosis, treatment and prognosis determination);

(6) Enable more quantitative criteria to be utilized when evaluating the results of certain diagnostic procedures (such as ECG's, EEG's) and perform complicated calculations necessary for the proper interpretation of certain clinical measurement;

(7) Aid the important aspect of information retrieval; i.e., rapidly retrieve current information about new preventative measures, diagnostic techniques and specific treatment;

(8) Accumulate and recall desired aspects of a particular patient's record.

Let us turn now to two approaches used in computers to yield these possibilities:

(1) *Analog approach*[8]

The problem of diagnostic computation has been approached by defining each disease in terms of its symptoms and their relative significance in the characterization of that particular disease. These "definitions" are then converted into analogous resistive networks and are used as standards against which a group of symptoms representing an unknown disease can be compared. The specialized computer constructed for this purpose compares the unknown with each of the standards stored in the machine, and, if there is a match, it indicates with which standard or disease there is a match and to what extent a correlation exists between them. The machine compares the unknown with all of the standards even if a match is found early in the process so that if two or more possbilities exist they will all be indicated.

(2) *Statistical Approach*[9]

It frequently occurs that it is not feasible, or desirable, to make further tests to distinguish between alternative possible diagnoses. The problem then resolves itself into determining, in the light of the patient's present symptom complex, what is the probability that the patient has a particular disease complex. We are asking for a conditional probability, given the patient's symptom complex, of the probability of his having the disease complex, d*i*. This is frequently denoted by $P(di|sj)$, where the symbol to the right of the slash is the condition, and the symbol to the left of the slash is the occurrence whose conditional probability is desired.

The well-known Bayes' formula offers important information concerning the compositions of $P(di|sj)$. The formula is

$$P(di|sj) = \frac{P(di)\ P(sj|di)}{\underset{\text{all } k}{\text{Sigma}}\ P(dk)\ P(sj|dk)}$$

where $\underset{\text{all } k}{\text{Sigma}}$ indicates a summation over "all possible disease complexes d*k*" under consideration. Let us focus our attention on the two terms in the numerator, namely $P(di)\ P(sj|di)$, since the denominator merely acts as a normalization factor. The term $P(sj|di)$ is the probability of having the symptom complex s*j* when it is known that the patient has the particular disease complex d*i*. This is precisely what is described in medical textbooks when a particular disease is under consideration. Of course, textbooks do not at the present time assign numerical values to $P(sj|di)$, but they do state that associated with a certain disease particular symptoms are common, frequent, rare, and so forth. The reason that $P(sj|di)$ is discussed [rather than $P(di|sj)$] is that etiology of the symptoms is related to, or stems from, the disease. Thus, $P(sj|di)$;

i.e., the symptoms resulting from a disease; is a constant for the particular disease complex under consideration, being relatively independent of other circumstantial factors.

On the other hand, consider the term, P(d*i*). This is the probability that, of the particular population of patients involved, any particular patient has this disease complex, d*i*. By "particular population of patients", we mean that population from which the patients can be considered as chosen at random. For example, the population may be that of the entire United States, or that of a particular clinic in a particular hospital; in each case P(d*i*) will, in general, be different. This term relates the influence of geographical, seasonal, epidemological, social, and other such factors to the diagnosis. Thus, in the tropics one is more apt to find tropical disease; during an Asian flu epidemic, the symptoms of a cold are more likely to be relegated to Asian flu; some diseases, like poliomyelitis, have a seasonal variation, and so forth. A little reflection indicates clearly that both these factors—the circumstantial or local, and the constant relating to the disease-symptom syndrome—influence the diagnosis.

The above theory enables programmes to be written to yield diagnoses on a problematical basis.

CONCLUSION

How is all this to be useful to the practitioner? Eventually a large central unit will be set up with many easily accessible satellite units available for the practitioner. He will be able to search large libraries of journals and consult many specialists by "consulting" the computer, for the information from journals and specialists will be programmed into the computer's memory.

In conclusion, it might be noted that, among othe obstacles in the path leading to electronic medica diagnosis, there is the handicap that the finest electroni data processing machines are inherently inferior to ma in the number of computing and/or memory element by about 10^{10} to 10^{23}. However, some of man's 10^{1} elements are occupied with other matters such as pre judices, political convictions, anxieties, sex, wife, chil dren, and income tax. A computer has none of these Also, in man approximately 400,000 elements are los per day or over 70 years about 10^{10} units. Perhap the computer's 10^{10} units can make up this loss.

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Recent Advances

Echoencephalography

For the past ten years or more attempts have been made to apply to medical diagnosis the principles of ultrasonic flow detection which were firmly established in engineering practice. This article will deal with the use of ultrasound in the detection of intracranial expansivities and will omit other areas of application such as the eye, breast, abdomen, heart and bone.

The echogram is obtained by the following procedure. Vaseline or glycerine is applied to the unshaven head about 4-5 cm. above the external auditory meatus. The ultrasound transceiver, containing a piezoelectric crystal, is applied at 90° to the sagittal plane. Pulsed ultrasonic waves are emitted at an average frequency of 2 megacycles/second. As skull thickness increases, sound wave absorption also increases. Conseqently, if difficulty is encountered in penetrating the skull a lower frequency is used (1 Mc/sec). In infants higher frequencies can be used (4 Mc/sec) since there is less absorption. When an ultrasonic wave strikes the interface between two media of differing densities, some energy is reflected from the interface, some transmitted, and the remainder absorbed as heat. The reflected waves are picked up by the transceiver during the non-transmitting phase. This echo pulse is amplified and applied to the Y-plates of a cathode ray oscilloscope tube which has a linear time base. The echo appears as a vertical pulse on the screen and the horizontal displacement of the pulse indicates the distance of the reflecting surface from the receiver.

The normal echogram shows 3 pulses: (1) the initial complex due to crystal artefact and scalp and skull interferences, (2) the midline echo (M-echo), and (3) the reflection at the inner surface of the skull on the opposite side. The source of M-echo is presently a controversial issue. Leksell and Jeppson have found the M-echo to be due to the pineal body in adults, and the walls of the third ventricle, posterior part of the septum pellucidum, and inferior part of the longitudinal cerebral fissure in children. For comparison a corresponding echogram is recorded from the opposite side. Use is made of the M-echo position in the diagnosis of intracranial masses. Jeppson has calculated that the probability is 98% in adults and 95% in children that a shift of 2 mm. in the M-echo of the echo-encephalogram represents a true unilateral expansivity. Errors are due to skull asymmetry or to the calculation of the actual midline brain shift from the echogram distances which are on a smaller scale. Additional errors in the 8-15 year age group are due to lack of pineal calcification and increasing skull thickness.

Despite the sources of error, echoencephalography has certain advantages. The method is quick, simple, and accurate; the equipment is compact and easily movable; the patient suffers no harm, discomfort, or inconvenience; the examination is infinitely repeatable and, therefore, suitable for following clinical progress (eg., post-operative hematomata and edema); and, in small children, in selected cases the method is preferable to other diagnostic methods — angiography, encephalography — which require a general anaesthetic. Post-operative hematomata which occur within 24 hours after neurosurgery can be discovered by echoencephalography 14 hours before clinical evidence of increased intracranial pressure appears (ie, increased B.P., and decreased pulse, respiratory rate and consciousness levels). When time is essential, as in cases of acute head injury, the echogram lays an adequate foundation for immediate surgical treatment, if indicated (eg, intradural or extradural hematomata).

There are certain disadvantages to echoencephalography, the main one being that the method is coarse and at the present time does not allow for exact localization. Infratentorial masses are rarely diagnosed. In addition, symmetrically distributed supratentorial lesions and small frontal or parasagittal lesions are not demonstrable. Echoes from the falx cerebri may be easily recorded and mistaken for true equidistant M-echoes.

Although the method is presently limited, extensive research and development are being carried out to make echoencephalography a more important diagnostic device.

P. R. Forrest 6T6

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Abstracts

Smoking in Relation to Mortality and Morbidity

Hammond, E.C.: J. Nat. Cancer Inst. 32: 1161-1188. May 1964.

442,094 men aged 40-89 were traced for about 3 years and the following results were obtained.

(1) Death rates were much higher in cigarette smokers, in those who started smoking at an earlier age and in current smokers (as compared with ex-smokers).

(2) Death rates increased with the amount of cigarette smoking and degree of inhalation.

(3) Cause of death in smokers was much more likely to be from cancer of the lung, buccal cavity, pharynx, larynx, esophagus, bladder and pancreas; gastric ulcer; emphysema; and aortic aneurism.

(4) Coronary disease death rates were more highly related to cigarette smoking in middle-age than in old-age groups.

(5) Death rates of smokers and non-smokers were studied in relation to other factors — longevity of relatives, family history of cancer, exercise, sleep, race, religion, marital status, nervous tension and history of previous disease.

In all groups, death rates of men smoking over 20 cigarettes per day were considerably higher than in non-smokers.

M.T.

A Comparison of Direct and Indirect Methods in the Diagnosis of Hemolysis.

Seaton, D.A.: Scot. Med. J. 9: 197-200, May 1964.

Laboratory investigations used to assist in the diagnosis of increased hemolysis are the measurement of erythrocyte survival (by the radiochromium technique), the reticulocyte count and estimation of fecal urobilinogen. These methods were compared in 21 patients with various myeloproliferative diseases. The radiochromium method is still the most useful aid but it is time-consuming and requires special facilities.

Daily fecal urobilinogen above 250 mg was seen in only 4 of 16 patients and results depend on variations in reabsorption of urobilinogen from the bowel, the capacity of the liver to cope with an increased pigment load and the derivation of urobilinogen from non-hemoglobin sources. The reticulocyte count is almost always raised with increased hemolysis as is the number of nucleated red cells.

The author concludes that simple and less expensive techniques (reticulocyte count and identification of nucleated red cells) give sufficiently reliable indices of increased hemolysis when radiochromium methods are not available.

M.T

On Inspection - Answers

Figure 1:

1. The bacteriophage consists of a hexagonal head filled with nucleic acid, and a contractile tail which will inject this material. In Figure 1, two states of a bacteriophage are seen; one in which the head is in high contrast, the sheath expanded, and another in which the head is clear, the sheath contracted. The former represens the bacteriophage prior to injection of its nuclear material, the latter after injection. The phage protein envelope is discarded after injection.

Cell viruses are basically of 3 structural kinds. First are those which are polyhedral and possess cubic symmetry. These are icosahedral structures; i.e., 12 corners, 20 faces and 30 edges; and exhibit five-fold symmetry at any apex, three-fold symmetry around any face axis, and two-fold symmetry rotates about any edge axis; e.g., adenovirus, Herpes virus. Second, are those of helical structure; e.g., tobacco mosaic virus. Third are those of more complex or asymmetrical structure; e.g., pox and orf viruses. All cell viruses have a core of nucleic acid (though in some, notably the helical viruses, this nucleic acid is closely bound to the protein capsule), a capsule (*capsid*) composed of many identical protein capsomeres, and an outer membrane (*envelope*) surrounding the virus.

2. In Figure 1 we see the bacteriophages attached to the bacterial wall just prior to injection of their nuclear material. This is an example of *cellular adsorption* and *infection*. Figure 2 demonstrates the *multiplication* and *maturation* of the phages within the bacteria. The full viral life cycye is *inoculation, cellular adsorption, infection, multiplication, maturation, host cell release* and the *free viral phase*. The bacteriophage never gains entrance to a bacteria but rather infects by the injection of its nuclear material. If the phage-infected cell is broken open just after adsorption, no particles capable of infecting other bacteria are recovered. This suggests that the injected DNA is not infective on its own. In a typical case, after about 12 minutes infective material can be isolated. During the latent period; i.e., prior to cellular lysis; 2 distinct stages can be distinguished. During the first, termed *viral eclipse*, no infective phage is recovered. In the second, infective phage production proceeds at a constant rate. Early during the eclipse period a series of new enzymes for the production of phage materials appear. In the latter part of the eclipse phase, new specific phage DNA starts to be formed. This synthesis of phage DNA proceeds at a rate balanced by the rate at which phage DNA is removed from the "DNA pool" and transformed into infective phage particles by the addition of the phage protein coat. The bacteriophage is then ready for release. The whole life cycle is complete in about 20 minutes, and culminates in bacterial lysis.

3. It has been suggested that cell viruses are engulfed by the cell and have their protective protein coat digested away within the cell, releasing the nuclear material which will direct the synthesis of virus protein and nucleic acid. For this adsorption and penetration to occur, it is thought that the viral protein capsid is important, possibly because of specific receptor sites on the cell; e.g., *in vitro* polio virus can infect only primate cell cultures. It has been shown that some viruses, such as influenza, possess enzymes which attack cell wall mucopolysaccharides. Some authors have suggested that a cation charge on the virus is important for adsorption to occur.

Figure 2:

1. Two main hypotheses have been advanced for the origin of cancer. One assumes that mutation occurs in some cell of the body, enabling the cell to escape the normal regulating mechanisms of the organisms. The other suggests that cancers are due to the invasion of healthy cells by viruses. This second hypothesis is becoming more tenable for a number of reasons. We know that viruses need not immediately kill their hosts, and that often, instead of making more virus particles, the virus enters into a union with the cell's own nucleic acid, and becomes an integral part of the cell's activity and replication. This state of subdued and integrated activity is called *provirus*. Bacteria carrying a provirus are called *lysogenic*. It has been shown that it is possible by radiation and strong chemicals to induce a provirus to turn to the vegetative replicating state. These agents are also capable of producing cancer experimentally in mice. While in the provirus state, we know from progeny studies, that a number of different forms of genetic interaction between host and viral nucleic acid can take place. Mutation of host or viral nuclear material can occur. Transduction occurs when host genetic components are incorporated into the genetic makeup of the virus. An interesting genetic element, the *episome*, ("added body") has been proposed to account for genetic alterations in some bacteria and plants. This piece of genetic information may replicate autonomously of host nucleic acid ("non-integrated state") or replicate at the same rate as the host's chromosomes ("integrated state"). The significance of the provirus and episome are that they are pieces of genetic material arising outside the cell, capable of producing effects similar to those of cell mutation. From this brief outline it is easy to see that the hypotheses of cell mutation and viral infection as a basis to malignancy draw closer together.

The Journal gratefully acknowledges the assistance of Dr. A. F. Howatson, Princess Margaret Hospital, Toronto, in the preparation of "On Inspection".

Abstracts

Chemotherapy of Metastatic Liver Cancer by Prolonged Hepatic-Artery Infusion.

Sullivan, R.D., Norcross, J.W., Watkins, E.: New Eng. J. Med. 270: 321-327, Feb. 1964.

A report of 21 patients with advanced liver metastases treated with continuous infusion of anti-metabolic drugs into the hepatic artery.

Catheters were sewn into the hepatic artery after ligation of non-hepatic branches and these catheters were sometimes left *in situ* after treatment, with no subsequent complications. Agents infused included methotrexate with intramuscular folinic acid; 5-fluorouracil; 5-fluoro-2-deoxyuridine. Infusion was continued until satisfactory regression of the liver tumor was achieved or toxic effects were observed.

16 patients received adequate treatment; in 13 there was significant tumor regression but only 10 obtained appreciable clinical benefit. 3 patients died of hepatic coma as a result of treatment, 2 showed no clinical improvement and 1 died of myocardial infarction. Toxicity was rare and liver function tests improved after cessation of treatment.

M.T.

The Cerebrospinal Fluid Glutamic Oxaloacetic Transaminase Activity in Neurological Diseases.

Mellick, R.S., Bassett, R.L.: Lancet 1: 904-906, April 1964.

A study of the G.O.T. enzyme in 273 cases — 241 with neurological diseases and 32 psychiatric controls with no organic disturbance. Most common neurological conditions included multiple sclerosis, polyneuritis, cervical spondylosis, epilepsy and cerebral tumors.

Patients with cerebral tumors showed a significant increase in G.O.T. levels above the established normal of 14.9 ± 6.3 Sigma-Frankel unit. Epileptic patients showed an insignificant increase between attacks but a marked increase within 48 hours of a seizure. Elevations were also observed after acute vascular episodes but no changes were seen in the other conditions examined.

The authors showed no correlation between protein and G.O.T. levels and conclude a raised CSF - G.O.T. level to be the result of leakage of the enzyme from cerebral tissues after hypoxia to the brain.

M.T.

Book Review

DIAGNOSTIC VIROLOGY

Hsiung, G.O. 125 pp. Illust. Yale University Press, New Haven & London, 1964. $4.50

This 125 page, soft-covered, and wire bound manua was written to augment a practical post-graduate cours given at Yale University. It "introduces some of th essential characteristics of animal viruses associated wit human disease, with special reference to tissue cultur techniques."

The book has two main divisions. The first sectio describes in detail the preparation of primate and non primate tissue cultures. The role of viral contaminatio is emphasized with particular attention to the action o the simian virus groups on prepared tissue groups.

The second section is subdivided according to viru groups which include the enterovirus, arbovirus, myxo virus, measles, reovirus, adenovirus, herpes, and po groups.

With each virus there is a description of the viru groups, its specific cytopathologic effect on tissues specimens required for testing, and the tests which ar positive for the virus. Each test is described in detai once, and is referred to in later sections if applicable.

Of particular merit are the numerous, clear picture which accompany each lab test, and the charts whic compare the viruses and give the differential diagnosi according to the laboratory results.

From the undergraduate, or medical practitioner' viewpoint, the book is not of much practical value. A was the author's intention, diagnosis is emphasized, an clinical aspects disregarded. The discussions are limite to the common viruses, and omit all the rarer forms o viruses essential to a complete study of the subject.

In summary, this is a technical guide which shoul be used as a reference in laboratories of diagnosti virology.

J.E.K.

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Doctor: a lot has been written about Erythrocin's safety record... but have you compared its **over-all effectiveness** with tetracycline?

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Here's what happened: Over 90% of all the patients taking one drug or the other responded to treatment.

The study involved 200 patients picked at random. Diagnoses ran the full variety of respiratory infections: pneumonias, infected throats, ear infections, etc. Etiologic agents were mostly gram-positive organisms.

Dosage was alternated with 100 patients receiving each drug. All doses were within the recommended ranges. Clinical response was as follows:

Antibiotic	*Excellent*	*Good*	*Unsatisfactory*	*Side Effects*
Erythrocin	59	32	9	9
Tetracycline	63	30	7	14

Obviously, there was no quarrel with the results. The authors agreed both antibiotics would effectively treat the same common infections. However, they added —

". . . because erythromycin exerts greater antibacterial activity, is bactericidal, and has a much lower incidence of resistant organisms, it is reasoned that it offers less chance of relapse and the development of resistant bacterial strains."

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Precautions: Side effects are rare. If a patient should show signs of sensitivity, countermeasures (e.g. epinephrine, steroids, etc.) should be administered and the drug withdrawn. Professional literature available on request.

Dosage: Usual adult dose is 250 mg. q.i.d. Children's dosage is based on body weight.

1. Printz, P. A., et al., A Comparative Study of Erythromycin and Tetracycline in Common Bacterial Infections, Clin. Med., 71:1037, June 1964.

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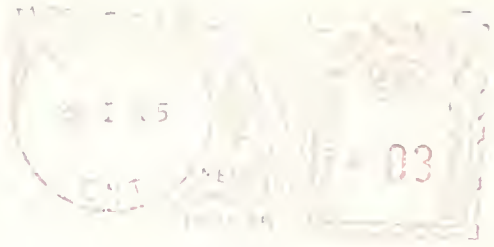

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